The Pharmacokinetics of Ketamine in the Breast Milk of Lactating Women: Quantification of ketamine and metabolites

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An NEIRB approved study

Clinical Trial Registration #

NCT04285684	The Pharmacodynamics of Ketamine in the Breast Milk of Lactating Women: (KRF-LAC)

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The authors confirm that the Principal Investigator for this study is Philip E Wolfson MD, and that he had direct clinical responsibility for patients.

Each of the authors state that there are no conflicts of interest and no relationships with commercial interests.

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Data is available by request from The Ketamine Research Foundation

Eligibility for Fast-track Review Service: There is no prior research available on this subject. As this research provides vital information to women who are breast feeding and are suffering from postpartum emotional disorders; or are breast feeding and have depression or other emotional disorders after the postpartum period, it provides information that will enable these women to continue their relationship with their infants without interruption while receiving ketamine treatment and especially ketamine assisted psychotherapy. This is in distinction to the continuous application of antidepressants and other treatments which have unknown effects on infant development, and pose a quandary for mothers to make a decision for such treatments.

Patient Informed Consent—IRB Approved—Full Document Included after References

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Abstract: There is no available data on the secretion and concentration of ketamine and its metabolites in breastmilk. There are statements in the literature made as to the safety of the use of ketamine in lactating women, though these are unsupported. This information is pertinent for the treatment of breastfeeding women who may have depression, PTSD, postpartum depression, and other emotional difficulties and would benefit from ketamine treatment. The objective of this study was to measure the presence and concentration of ketamine in breastmilk and three of its metabolites. We have provided a longitudinal pharmacokinetic analysis of the presence of ketamine and several of its major metabolites (norketamne, dehydronorketamine and hydronorketamine) in 4 women receiving 2 different intramuscular doses of ketamine—0.5mg/kg and 1.0mg/kg. Our results demonstrate the insignificance of ketamine's presence In breast milk after a 12-hour period of suspension. Given ketamine's proven record of effectiveness for the treatment of depression, and its intermittent use for this purpose, our data support the safety of its administration for the treatment of postpartum depression (PPD)and other emotional disorders during a woman's chosen period to provide breast milk to her child without significant interruption or exposure. This provides the necessary data for the study of ketamine assisted psychotherapy as a potential treatment of postpartum emotional disorders without the loss of the relationship between mother and child which breast feeding so vitally provides.

We review conventional pharmacologic treatments involved in the treatment of PPD in a section of this paper and examine its efficacy and potential impacts on nursing children.

Introduction

Ketamine was developed as an anesthetic agent, by Parke Davis, in the search for analogs resulting from recognition of the anesthetic properties of phencyclidine, the first drug developed in the arylcyclohexylamine structure during the late 1950s, 1960s. This drug was marketed as Sernyl and in addition to anesthesia, was also noted to cause significant increase in blood pressure and often prolonged postsurgical emergence delirium, even to the point of unmanageable, and at times, violent, 'manic behavior'. Ketamine was developed in the mid 1960s and was a successful anesthetic agent with fewer adverse effects than the parent compound. It was dubbed a 'dissociative anesthetic' by Antoinette, the wife of Edward Domino, the primary research clinician, as a solution to the descriptive puzzle offered by the drugs novel

effects.

Ketalar, ketamine's brand name, was approved by the FDA in 1970 for use in children, adults, the elderly and animals as an anesthetic agent. During the Vietnam War, ketamine became widely used as a field anesthetic administered to wounded soldiers because of its fast onset, lack of respiratory suppression, quick recovery period and its property of maintaining or elevating blood pressure in trauma situations (Morris, H. and Wallach, J, 2014; Lodge, DA. And Mercier, MS 2015; Wallch, J. and Brandt, S. D. 2018).

Ketamine's potential to treat different psychological or psychiatric problems commenced in 1974 in Argentina as an adjunct for antidepressant psychotherapy (Fontana 1974). In Mexico, the psychiatrist Salvador Roquet introduced ketamine to patients in group settings as a component of his approach to psychedelic psychotherapy (Kolp et al., 2007). And then he brought ketamine to the attention of investigators at the Maryland Psychiatric Research Center, Stan Grof and Bill Richards among them. Ketamine's versatility extends to analgesia and, for example, was used to treat patients who were at the scene of the 2005 London underground bombings. Following this awful act of terrorism, paramedics in the UK were authorized to possess and administer ketamine for pain relief.

Ketamine's tolerability and safety have been demonstrated over almost 5 decades. It has been used as an anesthetic for adults and children since the 1960s and has been used in neuropsychiatric research for more than two decades. Anesthetic doses from 1 to 4.5mg/kg are considered to be well tolerated and safe and as per the early Domino studies are often associated with dissociative experiences . Transient side effects including neurocognitive, sensory- motor, and hemodynamic changes can occur with subanesthetic doses of ketamine (from 0.1 to 2 mg/kg/IV) (Fourcade and Lapidus. 2016). A pooled data study from three different clinical trials of subanesthetic IV ketamine administration in MDD patients found that adverse effects common within the first four hours of administration included dizziness, derealization, and drowsiness (Wan et al. 2015). Whether these are truly to be considered 'adverse' or are part and parcel of ketamine's actual effects that result in the antidepressant and/or therapeutic benefits is the subject of much debate (Mathai et al. 2020). One third of all patients experienced transient hemodynamic changes, particularly elevated blood pressure. There have been no cases of persistent neuropsychiatric sequelae, medical effects, or increased substance abuse in clinical practice. Route of administration and dose provided will also affect tolerability. While there have been multiple reports of dissociative and psychotomimetic effects of ketamine with IV and IM preparations, a trial of sublingual ketamine in 27 MDD patients reported no such side effects (Lara et al., 2013). A trial of intranasal ketamine (50 mg) also found only small increases in dissociative symptoms (Lapidus et al., 2014). This appears to be contradicted by clinical experience that indicates significant dissociative effects with clinical benefit from these (Dore et al 2019) and may reflect the inadequacy of currently used rating scales.

A cautionary here in that increasing dosages of ketamine and resulting plasma concentrations through any route of administration will result in an increase in dissociative effects (Bowdle et al. 1998).

Ketamine is currently listed as one of the two injectable medicines under general anesthetics in the WHO Model List of Essential Medicines. The Model List designates medications determined "satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford" (WHO Technical Report

Series 2000). Ketamine was classified in 1999 as a Schedule 3 substance in the United States. Off label use has been a constant in ketamine's history.

Ketamine is in ever widening use for a variety of psychiatric disorders and its potency in improving and eliminating depressive disorders in sub-anesthetic doses has been extensively documented. Much of the expanding clinical use of ketamine has focused on its ability to exerts a potent and rapid antidepressant effect in patients with severe treatment resistant depression. (Bahji et al. 2020, Marcantoni et al. 2020).

Our group has specialized in the development of ketamine assisted psychotherapy and has pioneered and trained numerous practitioners in its use (Wolfson 2016, Dore, 2019). Our intention to study its effectiveness by extension to postpartum emotional disorders has depended on obtaining knowledge of its presence, and the length of its persistence in breast milk.

Post-Partum depression is a significant issue world-wide and effects up to 15% of mothers, with damage to families and collaterals. Evidence suggests that this condition is both under-recognized and under-treated. Moreover, treatment is often ineffective, and the complex persists causing long term harm to relationships. "There is a well-established relationship between untreated maternal depression and impaired child development (Murray ,L. and Cooper, PJ. 1997; Grace et al 2003)" Many clinicians have observed and written in this same vein: "PPD is associated with negative mother-infant interactions that include maternal withdrawal, disengagement, intrusion, and hostility.(Martina, C. and Gaffan, EA. 2000; Lovejoy, et al. 2000)"

Conventional treatment, particularly use of antidepressants and antipsychotics, exposes infants to continual absorption of medicines whose long term effects on development, and short term effects on mood and behavior are largely unknown (Osborne et al. 2020). Many women refuse to take these medicines for this reason. The second problem in this regard is the high degree of ineffectiveness of these medicines for many patients and the protracted time before therapeutic effects occur--when they do occur (Watkin et al. 2018).. This places the mother-infant dyad at risk during the extended period of time required for an antidepressant to achieve full effect.

We found only one paper in the literature pertaining to ketamine and PPD suggesting that prophylactic administration of ketamine intravenously at C-section would have a preventive effect on the incidence of PPD. This conclusion has been refuted by a subsequent more rigorous study (Xu et al 2017). There are several papers relating to ketamine's use as an anesthetic in combination for C-sections that are not relevant to this study or PPD.

Ketamine has been safely used as an anesthetic in pediatric indications for decades [Wilson et al. 1969, Greenbush et al. 2004] Reports on its safe use in obstetrics also exist [Moore et al. 1971, Little et al. 1972, Burke et al. 2016]. It was likewise posited to have no clinically relevant or adverse effects on neonates (Little et al., 1972). As this was early work and related to anesthesia, this remains an open issue for often repeated psychiatric use by pregnant or lactating mothers—which is the subject of this investigation. Establishing parameters for the presence and concentration of ketamine and its metabolites in breast milk has not as of yet been systematically quantified--until this study.

Pharmacology

Ketamine is available in two enantiomers: the S-(+)-ketamine (esketamine)and the R-(−)-ketamine (arketamine) configurations.. Most pharmacological preparations include an equimolar racemic mixture of the two enantiomers.

Although racemic ketamine has the broadest worldwide use, S(+)-ketamine is available in some European countries like Denmark, Finland, Germany and the Netherlands and came to market as a patented nasal preparation for psychiatric use in late 2018. Likewise, intranasal S-ketamine was recently approved in the United States as Spravato (Krystal et al. 2020). Spravato is FDA approved as an adjunct for TRD as well for the depressive symptoms in patients who are suicidal.

Ketamine's putative action is as an N-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist (Wallach and Brandt. 2018). Multiple routes of administration are utilized by practitioners treating depression and other psychiatric conditions, each with its own unique pharmacokinetics, have been investigated in the treatment of depression, including intravenous, intramuscular, intranasal, sublingual, anal, and oral delivery. He mechanism of ketamine's rapid acitng and sustained antidepressant activity still remains largely unknown. One of the leading hypotheses involves antagonism of NMDA receptors, which are widely expressed in the brain. When NMDA receptors on gamma-aminobutyric acid (GABA)-ergic neurons are antagonized, downstream glutamatergic neurons are disinhibited. This increased glutamatergic activity impacts neural signaling, synaptic plasticity, and connectivity. It is posited based on animal models that ketamine-induced synaptic potentiation and proliferation may play a key role in eliciting antidepressant effects. Other hypotheses exist as well (Zanos and Gould. 2018) Ketamine also impacts other neurotransmitter systems, affecting cholinergic, opioidergic, monoaminergic, and GABAergic function (Wallach and Brandt. 2018).

The bioavailability of Intramuscular ketamine is similar (93 -95%) to IV ketamine (Clements et al, 1982). Intranasal ketamine has been used in anesthesia and found to have a favorable pharmacokinetic and pharmacodynamic profile relative to oral and rectal administration (Costantino et al, 2007). In a blinded, randomized, controlled trial of 20 MDD patients, 50 mg of intranasal ketamine was found to elicit only mild side effects and produced significant antidepressant activity within 24 hours of administration (Lapidus et al, 2014). Estimates of intranasal absorption are variable ranging from 30-50%, with the lower figure seeming more the case in clinical practice. In several studies, Sublingual and oral ketamine have a calculated bioavailability of about 30 % and 20 %, respectively (Lara et al, 2013; Paslakis et al, 2010). In clinical practice, potency equivalence appears to be lower--20-30% for sublingual preparations and perhaps 10% for the oral administration. Of 27 patients with MDD given variable, escalating doses of sublingual ketamine, 20 experienced antidepressant efficacy (Lara et al, 2013). A retrospective review of 20 hospice patients receiving a single 0.5mg/dose of ketamine, given orally for 22 found significant antidepressant efficacy (Iglewicz, 2015). Ketamine is a weak base and thus is both water and lipid soluble. It is absorbable by IV, intramuscular, intranasal, subcutaneous, epidural, oral, and rectal routes of administration. Differences in the effects of ketamine are largely determined by the degree and rapidity of absorption and the rate of distribution to the central nervous system. Ketamine's relatively low binding capacity to plasma proteins may contribute to its rapid brain uptake and distribution (Weber et al. 2004).

Parenteral ketamine is rapidly distributed throughout the body into widely perfused tissues, including the brain. It is secreted into breast milk and does cross the placenta (Chang and Glazko 1974).

Pharmacokinetics

Ketamine has a low oral bioavailability of ~20% [Fourcade and Lapidus 2016, Dinis-Oliveira. 2017]. The major cause of low oral bioavailability is the first pass effect, believed to be to do extensive metabolism. CYP3A4 and CYP2B6 have been found to be the major enzymes involved in metabolic clearance of ketamine, with lesser contributions from CYP2C9 and CYP2C19 [Dinis-Oliveira. 2017]. The primary phase I metabolites of ketamine are norketamine, hydroxyketamine, various hydronorketamine isomers (HNK), and dehydroketamine (DHNK) [Desta et al. 2012, Dinis-Oliveira. 2017]. Extensive phase II glucuronidation, especially of hydronorketamine also occurs [Dinis-Oliveira. 2017]. Ketamine has been observed to have relatively low affinity for efflux transporters including p-glycoprotein (Pgp) [Keiser et al. 2017, Ganguly et al. 2018].

Ketamine has a relatively short elimination $T_{1/2}$ in humans with reported range from 79.8-186 min [Idvall et al. 1979, Clements and Nimmo. 1981]. Clearance rates have been reported from 720-1,680 ml/kg/hr [Domino et al. 1984, White et al. 1985, Geisslinger et al. 1993, Malinovsky et al. 1996] Because therapeutic ketamine is dosed infrequently [Jauhar and Morrison. 2019], plasma levels will not accumulate to a steady state and will rapidly decline due to ketamine's quick clearance rate. Most studies have found clearance rates of ketamine in pediatric populations to be comparable to adults [Elkomy et al. 2015]. Elkomy et al. 2015 failed to find age related differences in ketamine clearance rates (though notably most subjects were >1 year old). Notably younger and smaller children generally require higher infusion rates (and thus doses) of ketamine, relative to adults, to reach steady state levels for surgical anesthesia. This intriguing fact is believed to be due to the infusion to clearance ratio increasingly non-linearly with weight [Elkomy et al. 2015]. Consistent with this are the findings of an inverse relationship between weight adjusted clearance of ketamine and age [Herd and Anderson. 2007], an inverse relationship between age and ketamine dose for surgical anesthesia in children [Lockhart and Nelson, 1974], and a shorter duration of anesthesia in children relative to adults with 6 mg/kg IM ketamine [Nimmo and Clements. 1981].

Expression levels and activities of CYP2B6 can vary greatly between subjects [Croom et al. 2009, Pearce et al. 2016]. Likewise, CYP3A4 metabolism shows intrasubject variability [Özdemir et al. 2000]. Mixed evidence exists regarding the clinical relevance of CYP2B6 genotypes (e.g., CYP2B6*6 allele) in ketamine clearance with some finding no significant plasma or clinical differences [Li et al. 2015, Rao et al. 2016, Aroke et al. 2017]. One reason for the lack of clinically relevant activity in certain patients, may be the fact that other CYP enzymes may be able to compensate in many cases. Other factors may be related to dose, route of administration and other patient specific variables [Cook-Sather et al. 2016]. Ultimately, more work is needed and both CYP3A4 and CYP2B6 inhibitors can increase oral ketamine exposure (~2-3 fold) in human subjects [Peltoniemi et al. 2011, 2012].

Although age associated differences in CYP2B6 expression occur, with an increase in expression with age, detectable enzyme activity is seen immediately following birth [Croom et al. 2009, Pearce et al. 2016]. For example, Pearce et al. (2016) found that CYP2B6 activity could be detected as early as the first day or life, and increased through infancy reaching adult levels by one year of age. Adult levels were 2-5 fold greater than infant levels/activities [Pearce et al. 2016]. CYP3A4 shows similar age dependent increases, with mRNA expression being detected almost immediately post birth and enzyme activity reaching 30-40% of adult activity in liver microsomes after one month of age and peaking to comparable adult levels by one year [Lacroix et al. 1997].

Chronic abuse of ketamine has been associated with cognitive impairment, however this appears to be reversible as such findings were absent in ex-chronic users.(Morgan et al. 2009) While there is evidence of neurotoxicity from *in vitro* and non-human *in vivo* preclinical studies (Dong and Anand. 2013, Prakash et al. 2020), the translative validity of these findings to human clinical use remain unclear, and as Paracelsus wisely pointed out "only the dose makes the poison" (Gatenbein. 2017). While more work needs to be done to determine the clinical relevance of such findings, the therapeutic use of ketamine in pain, depression and as a general anesthetic have not been associated with demonstratable neurotoxicity or clinical findings of concern (Fourcade and Lapidus. 2016, Wais et al. 2020). Furthermore, as described previously, ketamine has been safely used at high doses as an anesthetic in obstetrics and pediatric indications [Wilson et al. 1969, Moore et al. 1971, Little et al., 1972, Greenbush et al. 2004, Burke et al. 2016, Prakash et al. 2020].

Pharmacodynamics

Two recent receptor binding studies evaluating affinities at over 57 and 80 pharmacologically binding sites on numerous receptors, channels, and transporters found that at concentrations below 10,000 nM ketamine only interacted with the PCP binding site of NMDARs [Roth et al. 2013, 2018, Salat et al. 2015]. Plasma levels of ketamine even after anesthetic doses (≥2 mg/kg) typically stay at or below 10,000 nM, especially following alpha phase distribution [Idvall et al. 1979, Geisslinger et al. 1993, Domino et al. 1982]. Lower potency effects have been reported at numerous other biological targets including opioid receptors, monoamine transporters, GABA and cation channels [Wallach and Brandt. 2018b]. However, given the low potency, these are of doubtful clinical relevance at physiologically relevant concentrations of ketamine [Wallach and Brandt. 2018b]. However, some higher potency effects (1-20 µM concentrations) have recently been observed including inhibition of hyperpolarization activated cyclic nucleotide gated channels (HCN) [Chen et al. 2009, Li et al. 2014] and relatively high affinity for the estrogen receptor alpha (ERα) (Kd = 344.5 nM) [Ho et al. 2018].

Ketamine's major pharmacological effects are associated with its ability to inhibit NMDARs. NMDARs are one of the major excitatory glutamatergic ion channels. NMDARs have been found to plays in development, synaptic plasticity, cell survival, learning, memory, processing of sensory information, and much more [Wallach and Brandt. 2018a, 2018b,

Morris and Wallach. 2014]. In addition to central populations, peripheral NMDARs also play important physiological roles, including functions in the immune system [Hogan-Cann and Anderson. 2016]. Ketamine acts as a use- and voltage dependent channel blocker [Lodge and Mercier. 2015, Wallach and Brandt. 2018b]. Ketamine's antidepressant, analgesic, anesthetic, anticonvulsant, neuroprotective etc. are believed to be mediated, at least in part, by NMDARs [Wallach and Brandt. 2018b, Lodge and Mercier. 2015].

Norketamine

The major active metabolite of ketamine is norketamine. Aside from NMDARs, norketamine lacked relevant binding affinity ((IC_{50} > 10,000 nM)) at 80 other pharmacologically relevant binding sites.[Salat et al. 2015] Importantly, norketamine has several fold lower potency than ketamine at NMDARs (e.g., ~6-fold lower affinity).[Ebert et al. 1997, Leung and Baillie. 1986, Moaddel et al. 2013]. Consistent with its lower NMDAR potency, norketamine has ~20-25% of the potency of ketamine in multiple murine models [Holtman et al. 2008, Sałat et al. 2015]. Norketamine partially inhibited agonist induced α7 nicotinic acetylcholine at 100 nM in KXα7R1 cells [Moaddel et al. 2013].

DHNK

No relevant affinities (>10 μM) were observed for dehydronorketamine at >80 binding sites evaluated including NMDARs. [Salat et al. 2015] However low affinity (>20 μM) at NMDARs for DHNK enantiomers has been observed. In addition, DHNK partially inhibited agonist induced α7 nicotinic acetylcholine at 100 nM in KXα7R1 cells [Moaddel et al. 2013].

Hydroxynorketamine isomers

HNK metabolites show substantially reduced affinity at NMDARs over ketamine and norketamine [Moaddel et al. 2013]. At 1-10 μM concentrations though (2R,6R)- and (2S,6S)-HNK inhibit LTP and fEPSPs seemingly through NMDARs [Kang et al. 2020].

A positive allosteric modulation on AMPARs by (2R,6R)-HNK at a 10 μM concentration was reported by Zanos et al. (2016). (2R,6R)-HNK also showed activity at the group II metabotropic glutamate receptors (mGluR2/3) [Zanos et al. 2019]. The clinical relevance of this is unclear, although some have speculated these metabolites may contribute to the antidepressant actions of ketamine based on findings in murine models [Zanos et al. 2016]. (2R,6R)- and (2S,6S)-HNK showed low uM affinities for ERα [Ho et al. 2018]

Research Design and Participants

This study was conducted with 4 lactating women who agreed to postpone breastfeeding and provide samples of their milk. Ketamine's half-life is variously placed at 2 and 1/2 to 3

hours. As an example, Herd et al (2002) found ketamine's half-life at 2.1 hours and for the potentially active metabolite—norketamine-- at 1.2 hours—this from a ketamine study in children that supported the safety of this medicine (Herd et al 2002). We collected samples of breast milk prior to injection for baseline measurement, and timed for pumping at 3, 6, 9 and 12 hours; i.e., 3 hour intervals--choosing the maximum half-life duration. Two dosages were administered Intramuscularly (IM) : first 0.5ml/kg and 1.0ml/kg. Each administration was separated by 5 days to two weeks.

The IM route was chosen as it confers rapid onset—2-5 minutes for effect and a reliable approximate 95% absorption of ketamine. The dosage range for a 50 kg woman amounts to 25-50 mg and for a 70 kg woman 35mg-70 mg, both quantities well within commonly used therapeutic administration of IM ketamine for depression and other psychiatric diagnoses (Dore et al, 2019).

Two of the investigators had close connections to practicing OB/GYNs, one having been one himself; and one had a practice with postpartum women at a local university medical school. As only 4 subjects were to take part, with the possibility of drop-out requiring further recruitment, this 'n' was compatible with the outreach potential of the Investigators. As lab analysis was to take place within days of each subject's session, the investigators were in a position to assess the consistency and range of results on an ongoing basis, allowing for a determination to add more subjects if the data suggested that need.

Potential lactating patients were approached for an initial screening conversation and if they met inclusion and exclusion criteria were admitted into the study. There were two rejections of potential subjects, one due to low weight and the other to revealing she was taking an anti-depressant long term.

Diversity of subjects: 2 women of Latina backgrounds, one Han Chinese woman and one Caucasian woman.

Inclusion Criteria:

- Age 21-45
- Postpartum with established lactation for a minimum of 3 months.
- Ability to pump breast milk and to provide a reservoir for infant feeding prior to the study; or acceptance of bottle feeding by the infant.
- In good health—normal BP/P; afebrile-temp ascertained; review of systems by MD; absence of diagnosed illnesses.
- Not pregnant--Pregnancy tested for before each administration by urine assay.

Exclusion Criteria:

- Hypertension with a BP greater than 145/90
- Subjects must be off all psychiatric medications specifically; medications and supplements, or evaluated by the PI for non-interference
- No alcohol or other substances such as marijuana for 72 hours or more.
- Weight <50kg or > 90kg.
- Pregnancy

Potential Adverse Effects—as explained to our subjects

- Nausea and vomiting—a less than 5% incidence of intolerability to ketamine.

- Transient hypertension—BP will be monitored. In clinical practice, and in this age group, this has not occurred with any significant frequency.

- Ketamine is a dissociative anesthetic and subjects had a high likelihood of experiencing dissociative effects during the first two hours following ketamine's administration. Generally, the major impact occurs in the first hour, with full recovery to baseline by 3 hours. The Investigators have conducted thousands of sessions in which dissociative effects are part of the ketamine assisted psychotherapy (KAP) approach, including at much higher doses than those being administered in this study. Subjects may and did experience, an altered mental state in which there was an imaginative stream of associations, sensations and imagery. This is dose related with the 0.5mg/kg dose having less of these effects. But ketamine, like other psychedelics, has as its core for effects an issue of personal sensitivity more than concentration by weight. These experiences may give rise to anxiety accompanying a shift from ordinary reality. The Investigators have specialized in developing a transformative psychotherapy with utilization of this state and are fully equipped and experienced in dealing effectively with this state. Subjects were prepared for the possibility of this occurring and did well with it.

Laboratory Analysis and Protocol

Quantitative analysis of ketamine and its metabolites was performed at the Clinical Medicine and Toxicology Laboratory at UCSF School of Medicine. Sample aliquots were frozen in our conventional freezer at the clinic where the sessions took place, labelled with a HIPAA compliant code which blinded the lab to all patient data.

Lab Methodology: Calibrators containing ketamine, norketamine, dehydronorketamine, and hydroxynorketamine (Cerriliant) were prepared in drug-free breast milk at 10 concentrations ranging from 0.1 – 100 ng/ml. Ketamine-D4 and Norketamine-D4 were used as internal standards. Breast milk samples (200 μl) were prepared using protein precipitation and EVOLUTE EXPRESS CX SPE cartridges (Biotage) following the manufacturers recommended protocol. LC-MS/MS data was acquired with a Sciex QTRAP4500 system in positive ion mode. Chromatographic separations were performed on a Waters XBridge BEH Phenyl XP Column (130Å, 2.5 µm, 2.1 mm X 50 mm) using a 4-minute linear gradient from 10%-33% with 0.1% formic acid in water and acetonitrile. The analytes were monitored using the following transitions (*m/z*) and retention times (min): ketamine 238.00→125.00, 89.00 (2.6), norketamine 242.00→129.00, 179.00 (2.10), dehydronorketamine 222.00→142.00, 177.00 (1.40), hydroxynorketamine 240.00→151.00, 124.00 (0.55), ketamine-D4 242.00→129.00 (2.60), and norketamine-D4 228.00→129.00 (2.10).

The limits of sensitivity for the quantification of each substance were:

Ketamine: 0.25 ng
Norketamine: 0.25 ng
Dehydronorketamine: 0.1 ng
Hydroxynorketamine: 0.25 ng

Methods

Subjects went through an intake and basic medical examination process. They were read a Script and an Informed Consent—IRB approved-- and engaged in a full set of discussions with staff prior to giving their written consent. A breast pump and collection supplies were provided and a private setting for pumping milk. A pregnancy test was administered prior to each session.

The administration of ketamine followed the basic protocol as per the clinic's practice of ketamine assisted psychotherapy (Dore et al 2019). An MD and a psychotherapist of same sex were present throughout the actual ketamine experience and during each collection, with ongoing support during the week following each session, availability thereafter, and a formal four week follow-up.

Subjects were instructed to express milk in full, this was collected, and the volumes measured. A sample aliquot was taken from each collection and frozen.

The lab processed the samples from the first subject as rapidly as possible to enable an estimate for the duration of the collection for subsequent subjects by quantifying the amount of ketamine present at intervals to 24 hours. As the amounts at 12 hours were insignificant, this led to a determination to collect milk at 3 hour intervals through 12 hours for the following 3 subjects.

Results

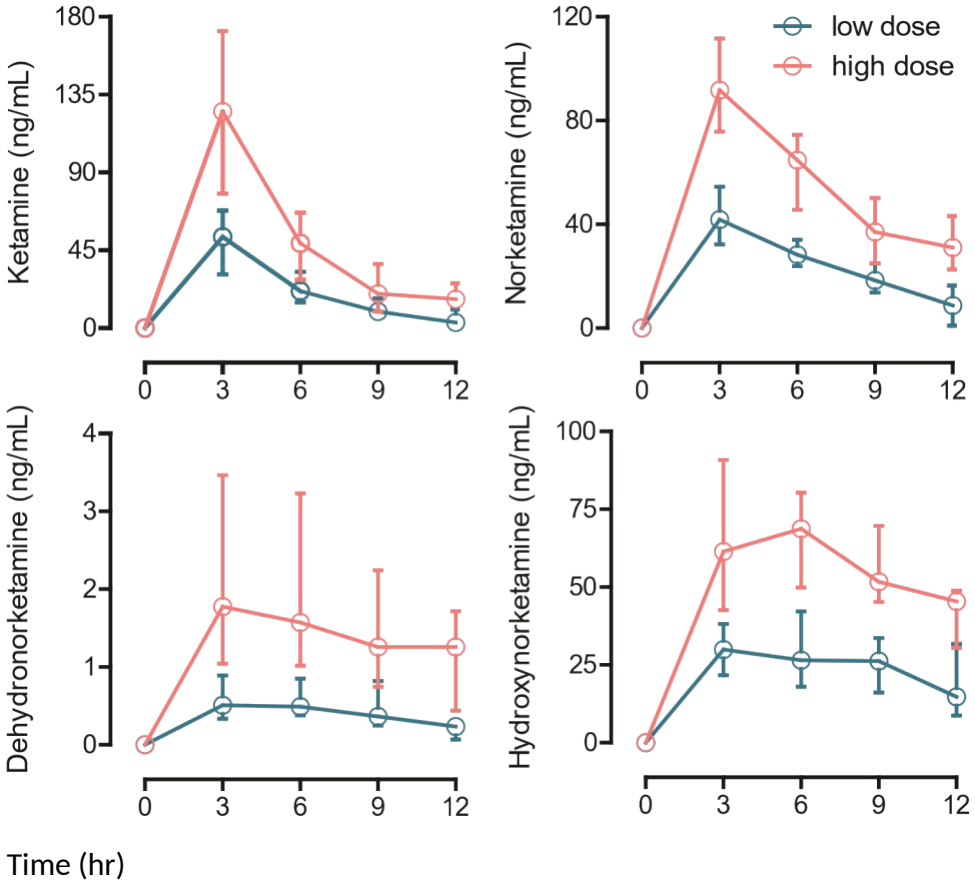
The Table of Results provides all data from our study and calculations of total ketamine and the 3 metabolites studied in each 3 hour interval per person and dose: 0.5mg and 1.0mg per subject.

Table of Results

Subject Code and dose	Date of Collection	Time of Collection/? At home	Volume	Fully expressed?	Results:K/Nor in ng/ml	Total Exposure Ketamine	Total Exposure Norketamine
1A1	12/20/2019	0	80	Y	0	0	
0.5mg/kg=31mg/IM	"	3	40	Y	66.407/48.138	2,656ng	1,926ng
		6	30	Y	26.37/32.12	791ng	963ng
		9	30	Y	12.78/21.054	383ng	632ng
		12	40	Y	10.672/16.334	427ng	653ng
		Next Day 24 houra	50	Y	5.042/8.55	252ng	428ng
1B2	01/03/20	0	100	Y	0	0	0
1.0mg/kg=60.5mg IM		3	38	Y	151.839/93.6	5,770ng	3,557ng
		6	25	Y	57.496/59.43	1,437.ng	1,486ng
		9	48	y	29.501/39.395	1,416ng	1,891ng
		12	30	Y	12.944/22.646	388ng	679ng
		24	128	Y	4.854/10.292	621ng	1,317ng
		30	53	Y	6.377/9.932	338ng	526ng
2A1	1/10/2020	0	235	Y	0	0	0
0.5mg/kg=28mg IM	"	3	115	Y	39.157/35.51	4,503ng	4,804ng
	"	6	80	Y	14.86/23.808	1,189ng	1,905ng
	"	9	82	Y	6.176/13.694	506ng	1,123ng
	"	12	95	Y	2.763/7.486	262ng	487ng
2B2		0	200				
1.0mg/kg=56mg IM		3	138		77.794/75.772	10,736ng	10,457ng
		6	64		27.927/45.564	1,787ng	1,405ng
		9	60		10.221/24.918	613ng	1,495ng
		12	NA				
3C1	1/27/2020	0	330	Y			
0.5mg/kg=26.3mg IM		3	180	Y	31.045/32.252	5,588ng	5805ng
		6	170	Y	15.515/24.432	2,638ng	4,153ng
		9	120	Y	6.351/15.66	762ng	1,879ng
		12	120	y	3.871/9.937	465ng	1,192ng
3C2							
1.0mg/kg=51.0mg IM	2/12/2020	0	140	y			
		3	140	y	98.612/89.949	13,806ng	12,593ng
		6	130	y	40.725/70.099	5,294ng	9,113ng
		9	130	y	9.606/34.757	1,249ng	4,518ng
		12	89	y	16.687/31.046	1,485ng	2,763ng
4D1							
0.5mg/kg=38.0mg IM	7/3/2020	0	90.5	y			
		3	90	y	67.991/54.954	6,120ng	4,946ng
		6	60	y	32.525./34.036	1,952ng	2,042ng
		9	70	y	17.264/24.967	1,208ng	1,748ng
		12	70	y	0.51/0.898	36ng	63ng
4D2							
1.0mg/kg=76mg IM	7/10/2020	0	90	y			
		3	88	y	171.825/111.64	15,121ng	9,824ng
		6	62	y	66.806/74.522	4,412ng	4,620ng
		9	60	y	37.165/50.179	2,223ng	3,010ng
		12	90	y	25.938/43.12	2,334ng	3,881ng
at 12 hrs;k +nork totals	1a 1.60mcg	1b 1.067mcg	2a 0.749mc	2b 2.108 mcg @9hrs	4a 0.09mcg	4b 6.22mcg	
total amount of k secreted in 12 hours		1a 4.26mcg of 31mg administred		1b 9.0mcg of 60.5mg admins			
		2a 6.46 mcg of 28mg admin		2b 13.13mcg of 56mg admin (9 hrs)			
		3a 9.45mcg of 26.3mg admin		3b 21.84mcg of 51mg admin			
		4a 9.32mcg of 38mg admin		4b 24.09mcg of 76mg admin			
total amount of norket secreted in 12 hours		1a 4.17mcg of 31mg admin		1b 7.61mcg of 60.5mg admin			
		2a 7.83mcg of 28mg admin		2b 13.36mcg of 56mg admin			
		3a 13.03mcg of 26.3mg admin		2b 28.99mcg of 51mg admin			
		4a 9;70mcg of 38mg admin		4b 21.33mcg of 76mg admin			
NOTE: KETAMINE AND NORKETAMINE SECRETION IS EXPRESSED IN MICROGRAMS							

Graphical description of each Subject's secretion in breast milk of ketamine and its metabolites with ranges for each time interval expressed in nanograms/ml.

Figure: Graphs of Quantitative Analysis for all 4 Subjects with Ranges



Following the curves for ketamine and norketamine quantities over time reveals the consistency of their metabolism, their linearity and rapid diminution in breast milk. Focusing on the maximum dose in a 76 kg subject, a total of 21.3 mcgs total was secreted over 12 hours with 15.1 *µgs* secreted in the first 3 hour sample. At the 9 hour collection 2.3 *µgs* total was found in the sample. Oral absorption by infants has not been studied, but if it follows the adult pattern, it would be 20% or less for ketamine present in the milk the baby imbibed (Fourcade and Lapidus 2016, Dinis-Oliveira. 2017).

If our small sample was not representative of the population at large and some women secreted at a 10 fold increase above our maximum concentration of ketamine, this would amount to 23 *µgs* in milk provided to an infant at 12 hours. Based on the consistency of our subjects' secretion, this seems more than unlikely. And in this example, the amount presented to an infant is insignificant and would be episodic in any treatment program utilizing KAP, or ketamine delivered without the therapeutic component we feel is necessary for best results and best connection to a symptomatic woman.

While psychiatric use of ketamine may well exceed 1.0 mg/kg, plasma concentrations of

ketamine for anesthetic use have tended to follow a linear pattern of concentration (Clements and Nimmo. 1981; Peltoniemi et al. 2016) and with our study enabling estimates of concentration in breast milk, should there be a decision to exceed 1.0 mg/kg IM in clinical practice, that expectation of similar relationship would be present. In fact, based on our robust clinical experience of the duration of ketamine's effects, it appears to not be extended by increases in dosage to any great extent

No adverse effects were reported by any of the 4 subjects for themselves or their infants.

Current Pharmacological Treatments of Post-Partum Depression

While our paper focuses on quantification of ketamine in breast milk over time, its significance is its vector towards a new and potentially highly successful treatment for postpartum emotional syndromes principally including the baby blues, postpartum depression and postpartum anxiety. As per our experience with ketamine assisted psychotherapy (Dore et al 2019), its potential role appears to us highly promising as a first line treatment choice for women making the difficult decision for opting for medication that will be absorbed by their infants with unknown long-term consequences on the future of their child's development, capacities and behavior (Sie et al, 2012)state "*Limited data are available about the long-term neurodevelopmental outcomes after SSRI exposure during pregnancy and lactation, but currently, cognitive development seems normal, while behavioral abnormalities may be increased*". Herein lies the dilemma for women and physicians treating postpartum depressive syndromes. In fact, data is so limited that no conclusions can be made about long term effects of SSRI treatment on either cognitive, behavioral or emotional results as there are no prospective studies, nor correlative ones of merit. In fact, it is not at all clear on what data this statement is made.

With current treatment options, this is the focus of important choices to be made by symptomatic mothers and their physicians and psychotherapists.

One of our authors (MW) puts this well:" In my clinical work with women who are having to make this choice, I see them face an impossible risk vs benefit scenario. Most societal norms instruct women to be "selfless;" they should put their children's needs before their own. If a new mother chooses to take an SSRI to treat symptoms of a postpartum mood disorder, she may worry she is being selfish. Ultimately, if a woman has significant fear about the risk to her infant, any benefit from the medicine itself may not be sufficient to treat the postpartum mood disorder. And she may fear that if she chooses to medicate, she will have to wean her baby off of breast feeding—a loss to both"

SSRIs continue to be the mainstay of treatment for PPD. While evidence exists to support the use of some SSRIs (Di Scalea et al. 2009, Carson. 2020), there remains controversy over their utility and the choice of a particular SSRI. Studies on the secretion of SSRIs in breast milk in infants give widely varying results and recommendations for safest SSRI. For example: *The amount of antidepressant concentrations to which neonates may be exposed, assessed as absolute infant dose (AID), was particularly low with the highest median AID being 0.16 mg/kg/day for venlafaxine. Findings suggest that breastfeeding under antidepressant treatment constantly exposes children with measurable drug concentrations* (Schoretsanitis G. et al 2019).

Assessing concentrations in breast milk of fluoxetine, sertraline, citalopram, and paroxetine from found concentrations, infant absolute (4.36-12.26 µg/kg/day) and relative dose (0.60-2.90%,) were estimated and low values were obtained indicating safe use during lactation (Salazar FR. Et al 2016). This statement appears to be only supported by an assertion. In fact, if one performs a 30 day calculation for exposure of a 3 kg infant breast fed on average six times per day, the total of exposure ranges from 0.392-1.103mgs. Obviously, exposure would be significantly higher as infants grow and breast feeding under the influence of SSRIs continues—usually for many months. Our concern needs to be an awareness that there may be risks to long term exposure during child development that have not been discerned due to the difficulty of studying this, and as such it is always ideal to keep exposure to a minimum.

As for claims made for the more recently introduced SNRI, duloxetine (Boyce et al 2011): '*Absolute infant dose via milk was 7.6 µg/L and relative infant dose was 0.81%.'* The conclusion that the relative infant dose via milk was low by comparison to most other antidepressants' appears to be misleading given the concentrations cited above which put this SNRI at midrange.

In contradiction a review of the literature by (Orsolini et al 2015) leads to this statement that '*Sertraline and paroxetine show a better neonatal safety profile during breastfeeding as compared with other SSRIs*' It is unclear how they can refer to a 'neonatal safety profile' when what is actually noted in this review is concentrations of SSRIs in mother's milk, the imputation then being to less potential exposure to the neonate.

Fluoxetine has also been implicated in case reports as causing colic, prolonged crying, vomiting, tremulousness and other symptoms as well as weight gain and in another study produced the highest proportion of infant levels elevated above 10% of the average level in mothers. It has been recommended against use in breast feeding as a result. Infant changes in metabolism of the drug at 12 months are said to reduce what has been estimated to be a very insignificant risk given that millions of breast feeding women have exposed their infants to this drug (Kendall-Tackett 2009) Additionally, they referred to a study, by Ref, indicating '*some potentially serious short-term effects have been noted in case reports of infants exposed to antidepressants via breastfeeding, but that the infant's symptoms correlated with withdrawal and re-exposure to the mother's breast milk*.

Of interest are two studies that examined the long-term effects of prenatal and postnatal exposure to SSRIs. Both studies included the same cohort of patients and conceptualized a notion of "behavioral teratogenicity", this at age 4 and potentially related to SSRI exposure in utero, and with breast feeding. Behavioral teratogenicity included internalizing and externalizing behaviors (Mistri et al 2006). Internalizing behaviors included emotional reactivity, depression, anxiety, irritability, and withdrawal. Externalizing behaviors included levels of activity, impulsiveness noncompliance, verbal and physical aggression, lowered task persistence, lowered problem solving, disruptive acts, and emotional outbursts (Oberlander et al 2007) The maternal exposure to medication was substantial, and included olanzapine for a subset of mothers with an average of 181 days of prenatal exposure and 60 days postnatal for SSRIs and 41 days postnatal for olanzapine. Mothers in the medication group had significantly more depression and anxiety at baseline and the majority remained symptomatic—with no further medication. At the 4-year visit, 59% of mothers had anxiety symptoms and 50% had depressive symptoms. Their infants were exposed to both the

effects of medications and ongoing maternal depression and anxiety. Of note is that despite treatment, such a high percentage of these mothers had ongoing depression. Current maternal depression and anxiety were more predictive of externalizing at age 4 than prenatal medication exposure. When the children were observed in a laboratory setting, those who were exposed to medication demonstrated significantly less persistence in completing tasks compared to children with no exposure. And poor neonatal adaptation predicted increased aggressiveness. When comparing the independent effects of prenatal medication exposure versus current maternal mood, the authors concluded that current maternal stress and mood were better predictors of externalizing behaviors, even after controlling for prenatal depressed mood or medication exposure. This study was the first to consider the dual role of prenatal SSRI exposure and current maternal mood. And it speaks to both the ineffectiveness of treatment and the effects on children at least at the 4 years of age mark of the persistence of maternal dysfunction—no surprise—and emphasizing the need for comprehensive and effective treatment which would impact both mothers and their offspring.

Gentile, S 2015 opines about SSRI treatment for depression citing for the postpartum period 'increased risks of neonatal complications, neuro-motor delay and even autism, this leading in part to *the 'bad reproductive reputation' of SSRIs, whose utilization during pregnancy and breastfeeding is deemed incautious'*. Unfortunately, studies that support what in essence is a speculative 'warning' are not available. There is great difficulty in performing long term prognostic studies due to the inability to adequately control major confounding factors of genetic and environmental nature. As is the usual advice, he then cautions that *' During puerperium, it is mandatory to weigh the risks to the infant of antidepressant exposure through breast milk against the disadvantage of not receiving mother's milk and being exposed to a relapse of maternal mood symptoms (which may also have tragic consequences for the patient)*.

(Fuguz F. 2018) cites the case of a neonate exposed through lactation at 2 months consecutively to sertraline, then paroxetine with resulting restlessness, and insomnia. Switching to citalopram led to remission of symptoms.

Compatibility of drugs with breastfeeding is another important consideration. '*Antidepressants should be avoided as much as possible due to their association with manic switches, rapid cycling, and suicidality. An important aspect of pharmacotherapy in women with a personal or family history of bipolar I disorder, **or** postpartum psychosis should be the management of insomnia that can either be an early symptom of, or a trigger for postpartum manic/mixed or psychotic episode* (Sharma, V. 2011).

In conclusion, contradictions abound on safest SSRI/SNRI for the neonate and the range of exposure cited overall is inconclusive for a recommendation. Suffice it to say that infants exposed to a constant stream of medication have relevant exposure over time no matter which antidepressant is chosen. And this cautionary may well need to extend to all psychoactive medications including ketamine and Spravato.

It is also important to state that there is support in the literature for the safety and use of existing antidepressants, citing the risks for not utilizing them when the impact is significant of

postpartum depression on maternal morbidity and its effects on the neonate (e.g., Di Scalea and Wisner 2009; Carson N. 2020).

SSRIs are notorious for their effects on both male and female sexuality and may add to the difficulty in the recovery of libido post-delivery. The course of postpartum sexuality is well described by Falicov, C as early as 1973 and this issue is important for further consideration by practitioners. Additionally, lactation's effect on sexuality has been documented in a number of studies, that include earlier psychoanalytically oriented interpretations ranging to actual studies (Sarlin 1981; Kayner 1983; Reamy 1985; Hughes 2008; Abdool 2009; Fuentealba-Torres 2019)

With respect to use of benzodiazepines and breastfeeding, indicating that adverse outcomes, specifically sedation, was identified in only 1.6% (2 of 124) of infants and was not associated with benzodiazepine dose, number of hours breastfed, or any demographic trait. Mothers reporting adverse outcomes in themselves (26% [32 of 124]) were more likely to be taking concomitantly a greater number of central nervous system depressants. Their conclusion was that this voluntarily reported study by mothers responding supported the continued (recommendation to initiate breastfeeding while taking benzodiazepines postpartum (Kelly et al 2012)

(Pons, et al 1994) review the use of conventional psychoactive medications and make the following prescient statement: "Drug excretion in breast milk depends mostly on passive diffusion of the unionised unbound drug. Passive diffusion is affected mainly by the drug disposition in lactating mothers, by the physicochemical properties of the molecule and by the protein and lipid contents of breast milk. Indeed, breast milk can be considered as a compartment with bidirectional transfer rather than a reservoir into which drug accumulates" They go on to recommend against breast feeding with high dose and prolonged administration of benzodiazepines, with phenobarbital, caution for signs of lithium toxicity in the neonate, and doxepin for its propensity for sedation

Because of its multiple effects during pregnancy and breast feeding, and its increasing public use as an inducer of compassion and social connection, oxytocin has entered into the treatment toolbox for postpartum emotional disorders. While there have been some suggestions on improvement in well-being, the data is controversial and as yet not convincing of utility (Kim et al 2013; Pratt et al 2015; Gu v. 2016; Mah et al 2016).

Estrogen treatment for PPD has come into fairly widespread use. A review study of treatment of Bipolar Disorder for PPD showed very low levels of estrogen in women with postpartum psychosis and significant improvement of symptoms after treatment with estrogen (Meinhard et al 2014). (Studd 2014) reports successful treatment with estrogen and testosterone in a portion of their sample and conclude that '*premenstrual and postnatal depressions appear in the same vulnerable women. These women are typically well during pregnancy and are a sub group of reproductive depression which also develops climacteric depression in the transition phase. These types of depression are the product of hormonal changes and respond well to transdermal hormone therapy'*

In a Cochrane review of the effects of dietary supplements on preventing PPD, (Miller et al 2013) find for insufficient evidence to conclude that selenium, DHA or EPA prevent

postnatal depression. Nor was there evidence to recommend any other dietary supplement for prevention of postnatal depression.

Thus, a review of available treatments for PPD and the emotional disorders of the post-natal period highlight the risks to the neonate and the unknown impact on child growth and development. The pervasiveness of PPD and its attendant suffering and disruptions, and given the limitations and side effects of current medications, the necessity for new and more effective treatments that pose minimal risk to both mother and child is clear. With no stigma when not possible, medicine and psychiatry need to support breast feeding as an essential aspect of child rearing

A recent development in the treatment of PPD is the FDA approval of brexanolone (allopregnanolone, Zulpresso™). Allopregnanolone, is a endogenous neurosteroid, whose levels have been found to drop after birth and this has been implicated in PPD (Meltzer-Brody and Kanes. 2020). Brexanolone shows rapid acting and sustained antidepressant actions. However, one limitation is it requires a 60 hour continues IV infusion (Faden and Citrome). 2020). The exact mechanism(s) of its antidepressant actions remain unclear, but it is posited to act through $GABA_A$ ion channels (via a positive allosteric mechanism of action) (Meltzer-Brody and Kanes. 2020). At least two studies have looked at the excretion of allopregnanolone in breast milk following a multi-day IV infusion (Hoffmann et al. 2019a, 2019b). Breast milk levels closely paralleled serum concentrations (71 mcg/L) likely due to the lipophilic nature of brexanolone. Breast milk levels fell to below the limit of detection (5 mcg/L) in most women by the third day post infusion. The prescriber information provided reports the amount of allopregnanolone secreted in break milk is low, representing 1-2% of the maternal dose. Of note allopregnanolone has low oral bioavailability which would further reducing infant exposure.

Discussion

Even with reduced enzymatic activity (and a resulting higher oral bioavailability), the low levels of exposure that would result from the levels seen in this study would not lead to clinically relevant effects in breast feed infants. For example, the highest amount of ketamine excreted over 12 hours post dosing was from patient 4 with the 76 mg dose. This was a cumulative 24 µg of ketamine and 21 µg norketamine. Assuming a 3 kg infant, this represents 1.6% or $1/63^{th}$ of a 0.5 mg/kg dose, or 0.4% and $1/250^{th}$ of a 2.0 mg/kg anesthetic dose of ketamine. A clinically relevant response is thus highly doubtful even if feeding is uninterrupted. Norketamine is about $1/4^{th}$ the potency of ketamine [Holtman et al. 2008, Sałat et al. 2015] and thus would also lack any clinically relevant activity at these dose levels.

A criticism of this study may be made regarding our sample size, namely 4. In response, the consistency of the amounts of secretion for both doses, the linearity of the metabolism and the insignificant amounts of ketamine and norketamine present after 3 hours support the generalizability of these findings. Hypothetically, a 100 kg woman adding a third more dose and a third more secretion would increase the amounts secreted but this

would still be insignificant at the longer intervals. Assuming an unusual woman secreted ten times the amounts herein reported, this would still be insignificant as withholding feeding went on

We are not making a recommendation for the length of time to withhold breast feeding. The data gives the story. Certainly, based on our findings, resuming breast feeding after pumping for 12 hours provides insignificant exposure for nursing infants.

Our data provides the first quantification of breast milk and ketamine's metabolism. This represents the first step to begin to systematically study the potential role ketamine and Ketamine Assisted Psychotherapy (KAP) may well have on postpartum emotional disorders.

It is our hope that with further study an important new method to treat postpartum depression and other postpartum emotional disorders will become available to postpartum patients. This becomes particularly appealing because of the rapid onset of this medicine, its therapeutic potential with its minimal neonatal exposure to exogenous therapeutics. Our grounded argument that KAP will be efficacious and a positive alternative to conventional treatment needs to be demonstrated for this population. With the data from this study, we are able to proceed.

And this is an urgent need. Postpartum depression continues to be a significant world-wide problem having far reaching impacts on the neonatal-maternal dyad and the involved family. With the unique therapeutic signature of KAP as it will relate to maternal anxiety and depression and embedded in a family systems support methodology, we believe there is great promise for women suffering with postpartum emotional difficulties.

Finally, not all emotional issues arising during breast feeding are of a postpartum origin. Many women breast feed for several years and may suffer with depression during that time. Our study gives beneficial information for the clinical use of ketamine when breast feeding-- no matter the causation.

Conclusion

The pharmacokinetics of ketamine in breast milk were presented. These findings show small concentrations of ketamine in breast milk with a rapid decline in breast milk concentration within hours. This supports the possibility for lactating mothers to resume feeding their infants after only a brief interruption of some hours' duration following administration of ketamine. This finding opens the door to the exploration of ketamine assisted psychotherapy for the treatment of emotional disorders of the postpartum period. As ketamine has potent antidepressant properties, the extension of its use to this pervasive problem is of great potential benefit. Short- term intermittent use of ketamine stands in contrast to use of conventional continuous administration of antidepressants and thereby potentially offers symptomatic women a new choice for their treatment without disruption of the mother-child nurturing relationship of which breast feeding is a fundamental aspect.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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RESEARCH SUBJECT CONSENT FORM

Title: ***The Pharmacodynamics of Ketamine in the Breast Milk of Lactating Women: Quantification Over 3 Half-Life Intervals of 3 Hours Each***

Protocol No.: PP1

Sponsor: The Ketamine Research Foundation

Investigator: **Philip E Wolfson MD**
6 Crest Avenue
San Anselmo, CA 94960
USA

Study-Related Phone Number(s): 415-550-1700; 415-309-0578 (minimal risk)

RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last 2 days separated by at least an interval of 3 days and up to two weeks.

Why is this research being done?

Purpose: There is no available data on presence and concentration of ketamine in breastmilk. This information is pertinent for the treatment of women who are lactating who may have depression, PTSD, postpartum depression, and other emotional difficulties and would potentially benefit from ketamine treatment. This study will assess if the rapid elimination of ketamine facilitates a short and tolerable suspension of breastfeeding. The use of ketamine in this study is investigational.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, the general procedures include receiving two injections intramuscularly of ketamine at sub-anesthetic low dosages based on

body weight, given in two separate sessions. You will be asked to pump your breast milk into containers before each injection and at 3, 6 and 9 hour intervals after receiving each injection. It may be possible that additional samples will be needed if ketamine is still detected. You will be attended two by two licensed practitioners including an MD, this taking place in a comfortable office setting. You will experience the ketamine effect for about an hour with a subsequent recovery period. You can expect to be at the study site for at least 10 hours on each occasion. You will begin with an empty stomach and after recovery will be provided with healthy foods of your choosing. You may have friends or relatives present to support you. Any emotional responses to the medicine are open to processing with staff. You will not be able to breastfeed your baby during the nine hours of each active portion of the study, or possibly longer.

Could being in this research hurt me?

The most frequent risks or discomforts that you may expect from taking part in this research include possible nausea and vomiting, the latter occurring in less than 5% of recipients of ketamine administered in this manner. You may experience transient hypertension and there is a possibility you may become agitated for a short time during the peak period of the ketamine experience. Our staff is present at all times to assist you.

Will being in this research benefit me?

You may or may not benefit. Possible benefits to others include providing information on the concentration of ketamine in mother's milk that will enable ketamine assisted psychotherapy treatment of women suffering with postpartum symptoms.

What else should I know about this research?

Ketamine is in widespread use for anesthesia, analgesia and now for over a decade as a treatment for depression, PTSD, OCS, and many other psychiatric and emotional difficulties. The researchers in your study have had experience with hundreds of patients, and many thousands of ketamine sessions. The explicit overarching goal of this research is to extend ketamine assisted psychotherapy to women having significant postpartum depression.

DETAILED RESEARCH CONSENT

You are being invited to take part in a research study. A person who takes part in a research study is called a research subject, or research participant. In this study, you will have some degree of an altered mind experience. This may include eyes closed visual hallucinations. Ketamine tends to induce positive moods, but you may pass through a difficult and transient internal experience. You may not wish to participate in the study because you fear loss of control of your mind, however transient, and however well supported by study staff. You will be with trained staff for at least 10 hours each day, of which the initial hour or so is the predominant altered state. Staff are skilled psychotherapists, versed in the practice of ketamine assisted psychotherapy. If emotional issues arise these will be fully processed.

Ketamine is a legal, Schedule 3 substance and is in use worldwide. Recently, the FDA approved intranasal ketamine for depression. The ketamine provided to you is considered to be an off-label, investigational use.

About 4 subjects will take part in this research.

What should I know about this research?

- Someone will explain this research to you.

- This form sums up that explanation.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

We expect that your taking part in this research will last 2 days of actual exposure to ketamine and breast pumping; plus an intake visit and follow-up sessions that will last several hours in total. A per your availability, you will have the two sessions 5 days or more apart and we would hope within two weeks. You will be followed for 4 weeks intensively and the investigators will be available as long as you may need to make contact. You will be given a copy of the findings of the study as this becomes available.

PROCEDURE TIMING CHART

HOUR	**PROCEDURE**
-30 minutes	Arrives at Study Site Pregnancy Test Review of IC and Fasting with Consent
-5	BP, HR, Review of Systems
0 Hour	Zero Time Pump
15	IM 0.5mg/kg; or Second Session 1.0mg/kg
15-60	Support for Subject who is reclining on sofa with eyeshades and ambient music
1 hour	BP, HR
1-3 hours	Support for subject and integration of experience
3 hours	BP, HR, Second Pump
3-6 hours	Subject relaxing at Study Site
6 hours	Third Pump
9 hours	Fourth Pump
12 hours	Fifth Pump if necessary (as per procedures)
Home	Milk has been quantified for volume at each pump and an aliquot labelled, saved and refrigerated. If subject has gone home earlier—at 6 hours or later, subject will be contacted to pump at the assigned intervals and an aliquot refrigerated for pickup and delivery to the clinical lab for analysis.

What happens to me if I agree to take part in this research?

You will meet with our study team, be interviewed, fill out confidential forms, have all your questions answered, agree to the study and sign an Informed Consent. You will be scheduled to spend two days with our Study Team and receive ketamine injections on two separate occasions based on your body weight. You will have agreed to provide 4 samples of breast milk during each of your days—one prior to the injection and 3 at separate intervals. You will be followed by our team for at least 4 weeks after your last session—and as long as necessary.

The study location is at our clinical site in San Anselmo, California—a comfortable office setting specifically designed for ketamine assisted psychotherapy.

You will be given an Intake Form to precede admission into the Study that includes a Questionnaire and the Informed Consent. If you wish, you will be provided the results of the Study in an anonymous format.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible to:

- Fast the morning of your sessions.
- You may have a cup of coffee/ or its equivalent in water or juice 3 hours prior to the session.
- You will have to refrain from alcohol and marijuana for at least two days prior to the study.
- You will not breastfeed your baby on the 2 days on which you have the ketamine injection, and maybe longer, depending on how long the ketamine stays in the breast milk.
- You will be tested for pregnancy prior to each injection of ketamine.
- You will be asked to provide information on any new medications prescribed to you prior to taking these—prior to and during the actual period of providing breast milk samples—and any medical issues arising during this period.
- If you have any emotional difficulties that you might attribute to your ketamine experiences, please contact your Study Team.
- You will be asked to provide 4 expressions of breast milk in each session.
- You must have someone to drive you home after each ketamine session.

Could being in this research hurt me?

The most important risks or discomforts that you may expect from taking part in this research include possible nausea and vomiting, the latter occurring in less than 5% of recipients of ketamine administered in this manner. You may experience transient hypertension and there is a possibility you may become agitated for a short time during the peak period of the ketamine experience. Our staff is present at all times to assist you. Agitation is treated by emotional support and non-intrusive reassuring touch to shoulders or hands, your consent having been given before the injection verbally. During the active medicine period of the session, two staff persons will be present with you. Staff provide for

your physical safety and well-being should you become agitated. During that time, you will be lying on a comfortable couch at a 45 degree angle, with a blanket, eyeshades and music—either ambient or headphones. In the rare event—we have never had this experience in thousands of sessions with ketamine—of severe agitation, you may be given a lorazepam lozenge.

Ketamine administered in this clinical environment may well contribute to a sense of well-being and an exploration of consciousness. You may expect to have dissociative effects that include inner visions, and a sense of being out of your body, and in less contact with your external sensations. This relates to the anesthetic properties of ketamine, present to a smaller extent than if you were having anesthesia. The doses used for this study are magnitudes less than those used for anesthesia. Staff is always present to support you should you feel confused by the changes to your consciousness, which generally are over within 45 minutes to an hour.

You will be administered an injection of ketamine intramuscularly in your shoulder or buttocks. You may feel a slight ache in the area for up to a few hours subsequently. The volume of the injection will be less that 1cc so there is minimal pain on injection or disruption of your tissue.

You may feel inconvenienced by not being able to breast feed.

Will it cost me money to take part in this research?

There is no cost to you to take part in this research study.

KRF will cover your travel costs and provide a stipend of $200—half of which will be paid at Admission and half at conclusion of the second session. If you decide to leave the study early, you will be paid for each visit that you completed.

Will being in this research benefit me?

We cannot promise any benefits to you or others from your taking part in this research. Possible benefits to others include providing information on the concentration of ketamine in mother's milk that will enable ketamine assisted psychotherapy treatment of women suffering with postpartum depression.

What other choices do I have besides taking part in this research?

This research is not designed to diagnose, treat or prevent any disease. Your alternative is to not take part in the research.

What happens to the information collected for this research?

Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor.
- People who work with the research sponsor
- The Institutional Review Board (IRB) that reviewed this research
- The Food and Drug Administration

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (800) 232-9570, info@neirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?

If you become sick, injured, or have an emotional reaction because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. The sponsor will pay any charges that are not covered by insurance policy or the government, provided the injury was not due to an underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study doctor or sponsor.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- It is in your best interest
- You have a side effect that requires stopping the research
- You are unable to take the research medication
- You are unable to keep your scheduled appointments

What happens if I agree to be in this research, but I change my mind later?

If you decide to leave this research, contact the research team.

Will I be paid for taking part in this research?

KRF will cover your travel costs and provide a stipend of $200—half of which will be paid at Admission and half at conclusion of the second session.

Your signature documents your consent to take part in this research.

Signature of adult subject capable of consent	Date
Printed Name of adult subject capable of consent	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	