

# The Prudent Prescriber

Phil Mohler, M.D. • pmohler69@gmail.com

2775 Crossroads Blvd • P.O. Box 10600 • Grand Junction, CO 81502-5600

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Pharm Reps  $\neq$  Rational Prescribing

(PR)



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### Ketamine for Depression Is Enthusiasm Ahead of Science?

In San Antonio, Texas, Kalypso Wellness promotes IV ketamine for two dozen conditions, including depression, cancer related pain, and lupus. One national chain of clinics markets their IV ketamine infusions, "The path to happiness begins with the first session." Without much looking, closer to home, I found three different groups of physicians in my own community offering ketamine for depression. I did not have a clue about this drug. Here's what the literature says about ketamine and depression.

#### History:

Ketamine has been available as an anesthetic agent for 45 years. However there are no post-marketing surveillance data on the use of ketamine for any psychiatric indication to provide information on long term safety or effectiveness. For a couple of decades, ketamine has been popular party drug.

Antibiotics do  
**NOT**

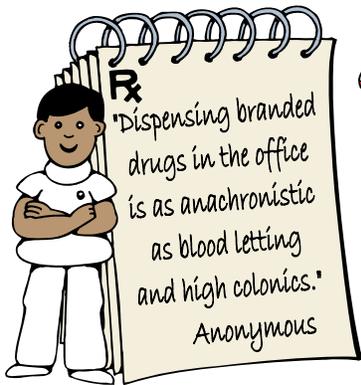


help  
acute bronchitis

**$\beta$ -blockers in  
post-MI  
save  
lives**



Pill splitters save  
BIG



**R**  
"Dispensing branded drugs in the office is as anachronistic as blood letting and high colonics."  
Anonymous



### CHE?

Think:

- Ace**
- Aldactone**
- B-blocker**
- Dig**
- Diuretic**



Avoid these expensive

"me-too" drugs:



- Intermezzo
- Vimovo
- Livalo
- Gralise
- Viibyrd
- Edarbi
- Daliresp

Treat patients  
> 60 years to 150/90



**NOW AVAILABLE  
ON THE  
GENERIC MARQUEE**

- Viagra  $\rightarrow$  sildenafil
- Effient  $\rightarrow$  prasugel
- Strattera  $\rightarrow$  atomoxetine
- Asacol HD  $\rightarrow$  mesalamine DR
- Pristiq  $\rightarrow$  desvenlafaxine

### **Mechanism of Action:**

In a study from Stanford, published in the August 29, 2018 The American Journal of Psychiatry, one of the principal authors Alan Schatzberg is quoted, “Now I know the drug (ketamine) works, but it doesn’t work like everyone thought it was working.” The Stanford scientists discovered the ketamine works as an antidepressant, at least in part, by activating the brain’s opioid system. This finding perhaps overturns the previously held belief that the drug’s antidepressant effects stem solely from its impact on the glutamate system. The researchers found that ketamine reduced depressive symptoms by 90% for three days in more than half of the 12 participants, but had virtually no effect on depressive symptoms when it was preceded by naltrexone.

### **Patient selection in the literature:**

The bulk of this scanty literature describes the effects of ketamine in patients with “treatment–refractory” major depression. The definition of treatment–refractory major depression and where treatments such as ketamine fall in the algorithm for management remains poorly understood. Is its niche: failed one antidepressant? failed two antidepressants? failed ECT? active suicidal ideation? All of these clinical scenarios have been studied in CLS (Crappy Little Studies) that leave us hanging with respect to efficacy and safety.

### **Dosing:**

- The presently used dose of 0.5 mg/kg of ketamine delivered intravenously over 40 minutes derives directly from a study by Krystal and colleagues (Archives of General Psychiatry.1994; 51 (3): 199 – 214.) in the late 1990s in which *they used this dose to induce psychotic and cognitive symptoms in healthy adults* (fortunately of short duration).
- Limited information is available regarding the use of different routes and delivery doses of ketamine. Currently, there are intranasal, sublingual and oral preparations being studied.
- Tolerance (tachyphylaxis) develops rapidly in frequent recreational users.
- Greater hemodynamic changes were observed in patients with a body mass index of 30 or higher suggesting adjusting ketamine doses to ideal body weight may be appropriate. There is currently very limited information regarding this approach.
- A major problem with ketamine is that its antidepressant effects following a single infusion are transient, usually abating in about one week or less. Efforts to prolong these effects involve repeated infusions or longer durations of infusion (e.g. four days). The risks and benefits of such alternative dosing regimens are poorly understood.

### **Studies:**

The Consensus Statement on the use of Ketamine in the Treatment of Mood Disorders (JAMA Psychiatry 2017; 74(4): 399–405) identified seven published, placebo-controlled, double blind, randomized clinical studies (**147 patients**) on ketamine infusion therapy in the treatment of depression. The authors conclude that these studies provide “compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient.” But read on, dear clinicians.

**Singh Study:** In a randomized, placebo-controlled clinical trial (using IV saline as the placebo) (Singh. American Journal of Psychiatry. 2016; 173(8): 816– 826.) 68 patients with treatment resistant major depression were given 0.5 mg/kg ketamine over 40 minutes IV either two or three times weekly for up to two weeks.

**Results:** For ketamine twice weekly, the 60 point Montgomery-Asberg Depression Rating Scale score (higher score is more depressed) fell 18.4 points vs 5.7 points for placebo. For ketamine three times weekly, the score decreased 17.7 points vs 3.1 for placebo. Patients treated with ketamine two times weekly showed a 69% rate of response and a 37.5% rate of remission versus placebo at 15% and 7.7% respectively. Those treated with ketamine three times weekly had a 53.8% rate of response and a 23.1% rate of remission versus placebo, at 6% and 0%.

Take home: This study suggests that twice weekly dosing is as efficacious as more frequent dosing. Most available reports describing the effects of repeated treatment showed the largest benefits occurring early in the course of treatment. (Shiroma. J Affect Disord. 2014; 155:123-129) Alas, this study went on for only 4 weeks, so we have no data regarding longer treatment.

### **Adverse Effects:**

- In reporting on 833 infusions in healthy individuals given a dose of 0.5 mg/kg over 40 minutes, Perry (Psychopharmacology. 2007: 192(2): 253 – 260) found three individuals who became non-responsive to verbal stimuli, but all remained medically stable during infusion.
- Long-term ketamine abuse is associated with cognitive impairment; whether that will be an issue with longer-term therapeutic dosing of ketamine is unknown.
- Transient mean increases in systolic blood pressure (19.6 mmHg) and diastolic blood pressure (13.4 mmHg) were reported during 205 infusions of 0.5 mg/kg of ketamine over 40 minutes in 84 otherwise healthy patients with depression. 30% of the patients treated developed blood pressures exceeding 180/100 mm Hg or heart rates exceeding 110 bpm. (Wan, Journal Clinical Psychiatry. 2015: 76 (3): 247– 252)
- A serious side effect in persons misusing ketamine is induction of ulcerative cystitis (so-called ketamine bladder). There are no reports of ketamine bladder in those who take ketamine less than daily. (Cottrell. BMJ. 2008; 336: 973.)
- In preclinical studies, ketamine has been associated with cell death in the developing central nervous systems of both rodents and rhesus monkeys. (Anesthesia 2012; 116:372 – 384). Additional evidence suggests that repeated ketamine administration to human infants may adversely affect neurodevelopment. (Journal Child Neurology 2014; 29: 1333–1338.)
- At present, there remains relatively little information regarding potential drug-drug interactions that could impact the safety or efficacy of ketamine treatment for mood disorders.
- Poverty

### **Costs:**

- One pain management clinic in Grand Junction is charging their patients \$500 per infusion plus an initial consultation fee.
- Ketamine is available at 8-33 cents per mg. The typical 80kg man would require 40mg per infusion, so drug costs are \$3.20-\$13 per infusion.

### **Ethical Issues:**

- Singh et al. in Lancet Psychiatry, vol. 4, May, 2017) has an extensive review of the ethical issues surrounding the use of ketamine in depression.

### **What's in the pipe line?**

Janssen Research and Development is studying the “s” isomer (esketamine) in an intranasal form for depression. Dr. Singh, who I have quoted above, has been an employee of and owned stock in Janssen.

### **My Take:**

- Researching the ketamine literature is a primer in evaluating drugs. These studies feature CLS: small “n”s, poor controls (the saline placebo recipients know what they are getting and drop out quickly), researcher conflicts of interest, short term studies (often less than a month) in a chronic disease and a lack of consensus regarding which patients are the best candidates for treatment.
- A challenge of off-label drug treatment is that the drug’s efficacy, dosing and side effects are interpreted largely through clinical experience and case studies, rather than through the gold standard of evidence provided by clinical trials.
- In reviewing what is written about ketamine’s use in depression, the phrases, “poorly understood,” “limited information,” and “insufficient data,” occur too frequently. The off-label clinical utilization of ketamine for depression is outpacing scientific scrutiny and may invite adverse sequelae that will exceed any therapeutic benefit.
- Perhaps most troubling are stories of patient self-referring, lack of established drug indication criteria, an absence of mental health providers in the process and poor communication with primary care physicians.

You may access previous issues at <https://www.rmhp.org/i-am-a-provider/provider-resources/publications-for-providers>.

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