

Background

Ketamine is a phencyclidine anesthetic that elicits its analgesic effects primarily through the antagonism of N-methyl-D-aspartate receptors [1-2]. During states of chronic pain, in which stimulation of NMDA receptors results in amplified trafficking of pain signals to the brain, ketamine blocks excessive nociceptive input [3-5]. This study seeks to elucidate the relationship between different dosages of oral ketamine and the incidence of adverse side effects by comparing three groups given long term prescriptions of 80-159 mg, 160-199 mg, or 200-240 mg of oral ketamine for chronic pain.

Methods

All adult patients given off-label prescriptions of oral ketamine from November 2019 to October 2023 were identified for our initial cohort. Patients were excluded if they failed to reach at least 80 mg per day during their treatment period or if their treatment periods lasted less than 90 days. Demographic variables, comorbidities, and prescription information were recorded. Patients were sorted into 3 groups: Group 1: 80-159 mg/day, Group 2: 160-199 mg/day, Group 3: 200-240 mg/day. The primary outcome was the number of adverse side effects, defined as patient-reported negative events from oral ketamine intake that resulted in a decrease in prescription dosage. Statistical analysis consisted of a generalized linear model. The present study was conducted as approved by the Institutional Review Board HS-23-00638.

Results

This study identified 193 patients who received long-term, moderate to high dose oral ketamine prescriptions for chronic pain at our institution between 2019 to 2023. 149 patients received 80-159 mg per day, 24 patients received 160-199 mg per day, and 20 patients received 200-240 mg per day. While Group 1 and Group 2 showed a difference in age ($P=0.02$), no significant differences were found when comparing BMI, sex, and count of comorbidities between the three groups. Of the 193 total patients, 20 separate instances of adverse side effects were documented by 13 separate patients, with certain patients reporting multiple side effects.

Table 1: Patient Demographics

	Demographics						P-value
	Group 1 80-159 mg N=149		Group 2 160-199 mg N=24		Group 3 200-240 mg N=20		
	Average	SD	Average	SD	Average	SD	
							Group 1-2 p = 0.02
Age (years)	49	15	57	13	48	14	Group 1-3 p = 0.96
BMI (kg/m2)	27	6	28	6	26	6	Group 3-2 p = 0.08
	Number	Percent	Number	Percent	Number	Percent	p = 0.475
Female Sex	110	73.82%	18	75.00%	11	55.00%	Group 1-2 p = 0.903
Male Sex	39	26.17%	6	25.00%	9	45.00%	Group 1-3 p= 0.200

Table 3: Count of Comorbidities

Group	Average Count of Comorbidities	SD of Comorbidities	# patient reported SEs
1	1.27	1.32	9
2	1.16	1.21	2
3	0.9	1.37	2
TOTAL	1.11	1.32	13

Table 4: Patient Side Effects

Group	Total # patients in each group	# patients reporting SEs	% patients reporting SEs	# separate instances of SEs
1	149	9	6.0%	12
2	24	2	8.3%	6
3	20	2	10.0%	2
TOTAL	193	13		20

Table 6: Treatment Period

Group	Average Length of Treatment Period (days)	# patients who showed no change or increase in ketamine dosage during treatment period	# patients who showed a decrease in ketamine dosage during treatment period	# separate instances a decrease in ketamine dosage was from no SE	# separate instances a decrease in ketamine dosage was from SEs
1	774	99	50	62	12
2	1002	16	8	14	6
3	792	12	8	10	2
TOTAL		127	66	86	20
AVG	856				

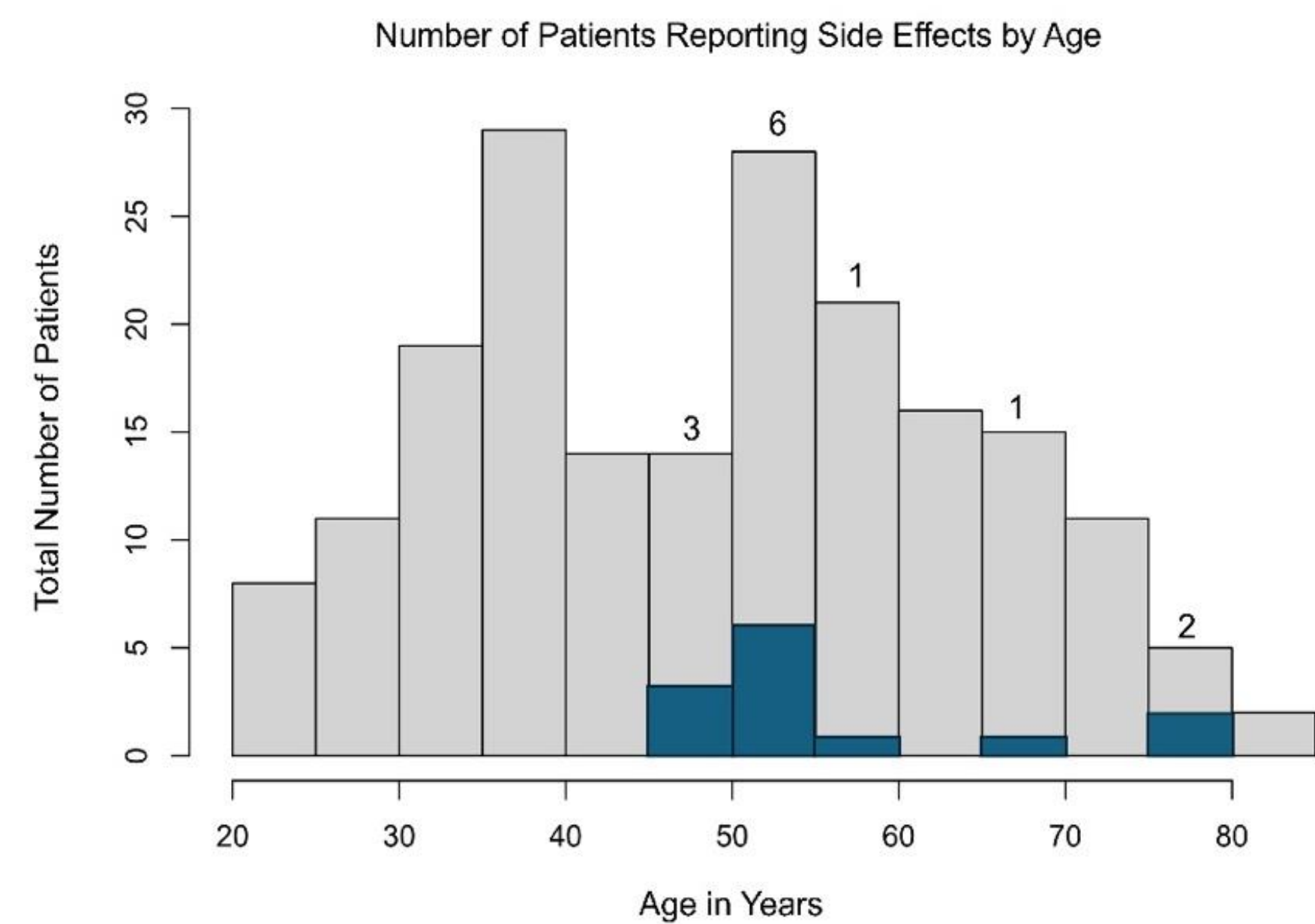


Figure X. Histogram of side effect occurrence by age. Reported side effects, represented by blue bars and the number above each age group. Side effects occurred in ages 45 and greater in our sample.

Table 2: Primary Diagnosis

Diagnosis	# Patients	% Patients
Central Neuropathic Pain	65	33.7
CRPS	64	33
Fibromyalgia	16	8
Migraine	12	6
Painful Limb Ischemia	1	0.5
Peripheral Neuropathy	17	8.8
Post Herpetic Neuralgia	2	1
TMJ Disorder	1	0.5
Trigeminal Neuralgia	1	0.5
Visceral Pain	14	7.2

Table 5: Types of Adverse Reactions

Adverse Reaction	# Patients*	% Patients
None	180	93.26%
Memory Difficulty	2	1.04%
Sedation	3	1.55%
Unusual Dreams	2	1.04%
Nausea	1	0.52%
Irritable Bladder	1	0.52%
Hair Loss	1	0.52%
Tachycardia	1	0.52%
Dizziness	2	1.04%
Fogginess	2	1.04%
Slurred Speech	1	0.52%
Insomnia	1	0.52%
Migraines	1	0.52%

*Some patients reported multiple side effects

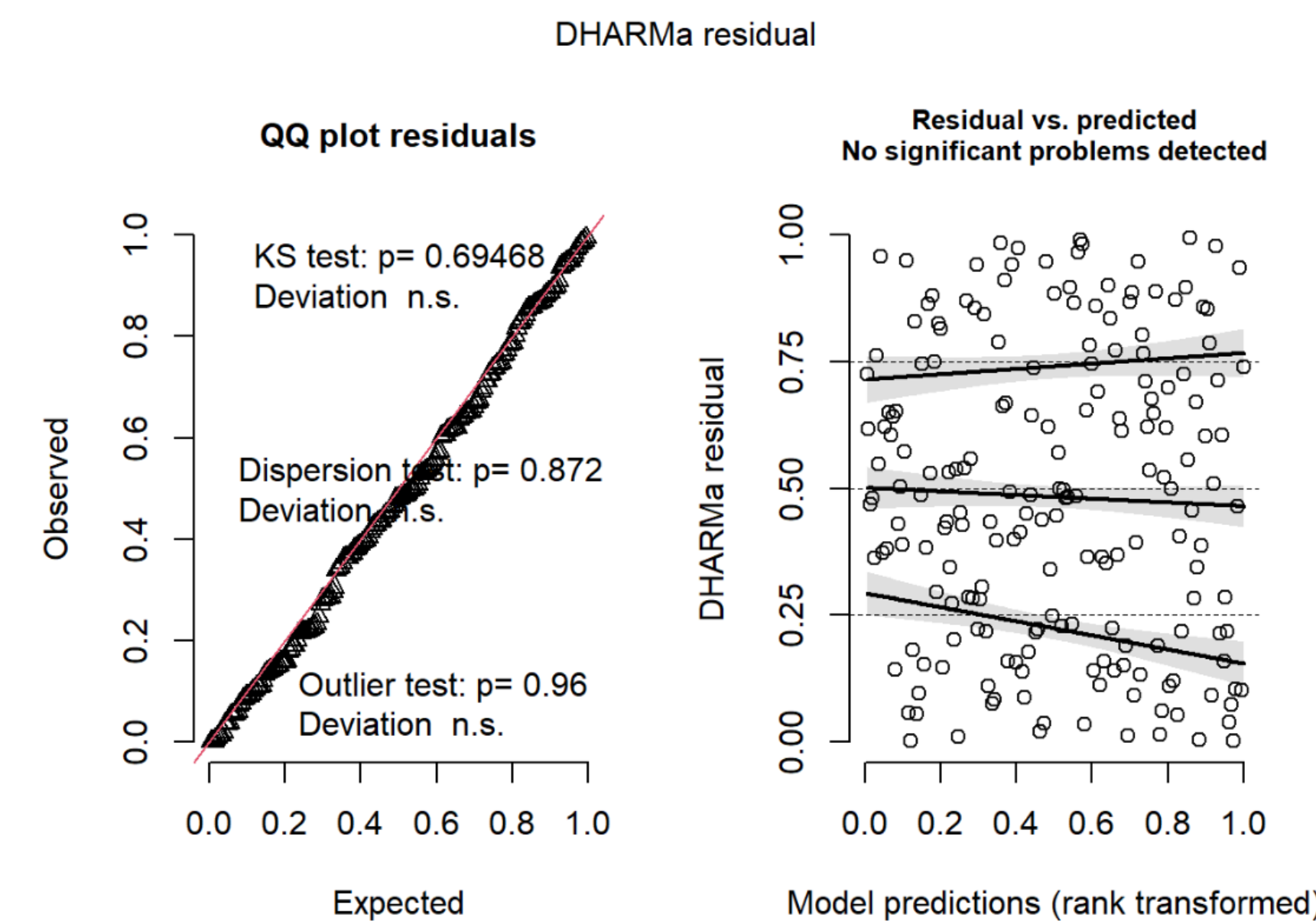


Figure Y. Diagnostic plots for generalized linear model. All tests performed in the R package DHARMa supported proper model fit for our negative binomially distributed generalized linear model.

In Group 1, 9 of the 149 patients (6.0%) reported 12 separate instances of adverse side effects. These included difficulty with memory, sedation, unusual dreams, nausea, irritable bladder, hair loss, tachycardia, and dizziness. In Group 2, 2 of the 24 patients (8.3%) reported 6 instances of adverse side effects, including sedation, fogginess, slurred speech, and dizziness. In Group 3, 2 of 20 patients (10%) reported 2 instances of adverse side effects, including insomnia and migraines. The average length of treatment for Group 1, 2, and 3 were 774 days, 1002 days, and 792 days, respectively. 127 patients (65.8%) in our cohort showed a slowly escalating or steady state of ketamine dosage throughout their treatment period, while 66 patients (34.2%) showed a decrease in ketamine dosage at some point in their treatment period. Of these 66 patients, 86 total instances (62 in Group 1, 14 in Group 2, 10 in Group 3) occurred in which a ketamine dosage was decreased not due to side effects versus 20 total instances occurred in which a ketamine dosage was decreased because of a side effect. No significant interactions between maximum average daily dose and other patient covariates were found. The maximum average daily dosage was not associated with the number of reported side effects ($P = 0.10$). Age was the only covariate significantly associated with the number of adverse side effects, as older patients were more likely to report side effects ($P = 0.04$).

Conclusions

- At daily doses above 80 mg and up to 240 mg, oral ketamine does not show a dose-dependent relationship to predict the number of patient-reported side effects.
- Increased age was associated with an increased incidence of adverse side effects from oral ketamine.
- Oral ketamine may serve as a safe opioid-sparing alternative for refractory chronic pain patients.

References

1. Yang, Y., Maher, D. P. & Cohen, S. P. Emerging concepts on the use of ketamine for chronic pain. *Expert Rev. Clin. Pharmacol.* **13**, 135–146 (2020).
2. Culp, C., Kim, H. K. & Abdi, S. Ketamine Use for Cancer and Chronic Pain Management. *Front. Pharmacol.* **11**, 599721 (2020).
3. Orhurhu, V., Orhurhu, M. S., Bhatia, A. & Cohen, S. P. Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Anesth. Analg.* **129**, 241–254 (2019).
4. Al Mukhaizeem, S. *et al.* Investigating the effectiveness of oral ketamine on pain, mood and quality of life in treatment resistant chronic pain. *Front. Pain Res.* **4**, 1268985 (2023).
5. Bell, R. F. & Kalso, E. A. Ketamine for pain management. *Pain Rep.* **3**, e674 (2018).