

Patient Willingness to Participate in Randomized Clinical Trials Involving Intravenous Perioperative Methadone: A Systematic Review

Janet O. Adeola MD¹, Ellen M. Soffin MD PhD², Ryan S. D’Souza MD³, Alexander B. Stone, MD¹

Affiliations

1. Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
2. Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, NY, USA
3. Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA



Introduction

- Methadone is a long-acting opioid that has a favorable pharmacokinetic profile for long acting perioperative analgesia.
- Despite recent studies which have demonstrated improved longer acting analgesia and a reduction in the need for postoperative short acting opioids, there is still hesitancy to use methadone perioperatively.
- As a result of its use for the treatment of opioid use disorder (OUD), methadone may have a stigma associated with it in the lay press and among the general population.
- We decided to undertake this systemic review to measure if there is a high rate of patient refusal to participate in perioperative methadone studies.

Material and Methods

- The inclusion criteria for screening were studies in humans that were prospective randomized controlled trials where one study arm was randomized to receive methadone as part of an analgesia pain.
- Exclusion criteria included any study where the full text was not available, and abstracts presented at meetings.
- Primary outcome: the ratio of the number of patients who declined to participate and the number of patients who were approached.
- Secondary outcome: was the ratio of the number of patients who declined to participate and the number of patients who were randomized. Data on the drop out rates, cross over rates, and lost to follow up rates were also collected.

Results

- 23 studies met our inclusion criteria for a full text search. Of the 23 studies that met inclusion criteria, only 9 (39.1%) reported the number of patients that refused to participate and were included in the analysis (Figure 1 & Table 1).
- The 9 trials that reported patient refusal rates, evaluated a total of 1631 patients of which 293 (18.0%) declined to participate.
- Those 9 studies eventually randomized a total of 964 patients making the refusal to randomization rate 30.4%.
- All of the studies that had ratios of refusal to approached greater than 0.20 were based in the United States (Table 1; Figure 2).

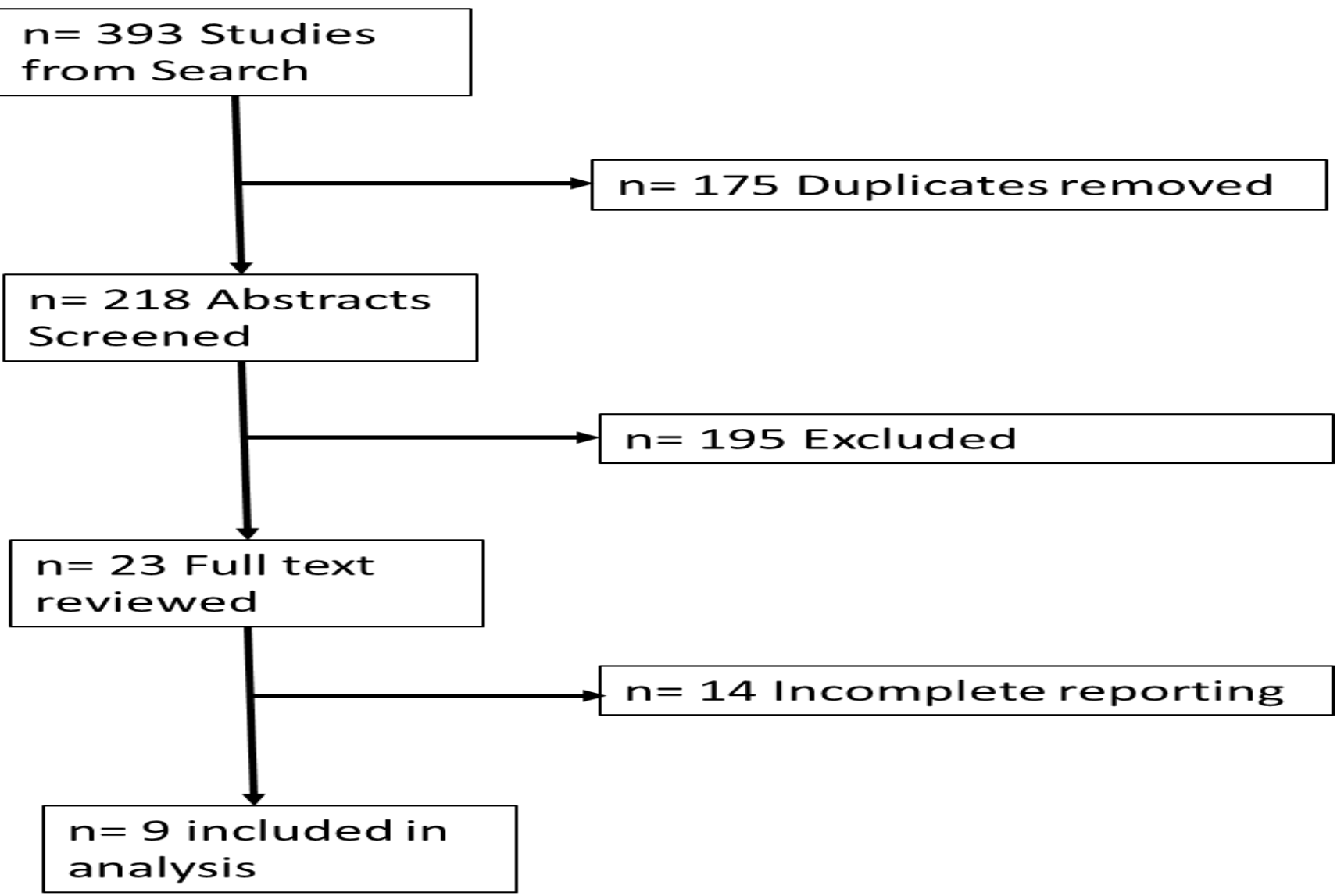


Figure 1: flow diagram outlining inclusion method in study

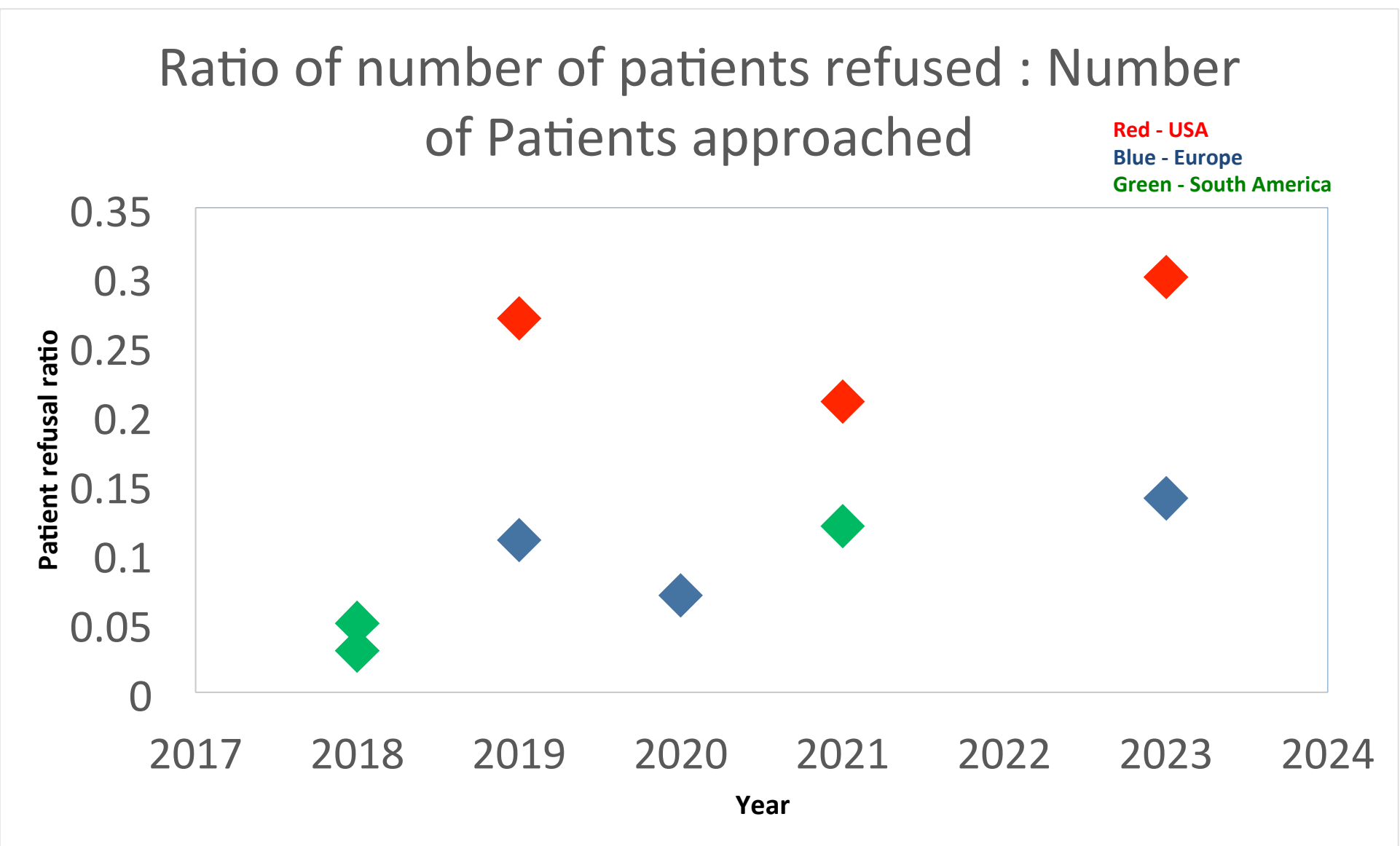


Figure 2: patient refusal ratio as a function of year and country

Author	Year	Country	# Patients assessed for eligibility	# Patients excluded (all reasons)	# Patients refused to participate	# Patients randomized	Ratio # patients refused/ # patients eligible	Ratio # patients refused/ # patients randomized
Kharasch	2023	USA	402	254	119	139	0.3	0.86
Komen	2019	USA	156	86	42	66	0.27	0.64
Murphy	2021	USA	177	47	37	130	0.21	0.28
Friisgaard	2023	Denmark	245	82	35	163	0.14	0.21
Bastian	2019	Switzerland	241	81	27	160	0.11	0.17
Pontes	2021	Brazil	194	54	23	140	0.12	0.16
Mercadente	2020	Italy	72	3	5	64	0.07	0.08
Moro	2018	Brazil	102	32	3	70	0.03	0.04
Machado	2018	Brazil	42	10	2	32	0.05	0.06

Table 1: studies with complete patient refusal and participation information

Author	Year	Country	# Patients assessed for eligibility	# Patients excluded (all reasons)	# Patients refused to participate	# Patients randomized	Ratio # patients refused/ # patients eligible	Ratio # patients refused/ # patients randomized
Khajavi	2023	Iran	90	5	NR	85		
Murphy	2017	USA	120	NR	NR	120		
Carvalho	2018	Brazil	145	32	NR	104		
Murphy	2015	USA	164	8	NR	156		
Gourlay	1982	Australia	NR	NR	NR	23		
Gourlay	1986	Australia	NR	NR	NR	20		
Chui	1995	China	NR	NR	NR	30		
Montazer	2021	Iran	NR	NR	NR	60		
Gottschalk	2011	USA	NR	NR	NR	30		
Richlin	1991	USA	NR	NR	NR	40		
Udelsmann	2011	Brazil	NR	NR	NR	55		
Berde	1991	USA	NR	NR	NR	35		
Martin	2018	USA	NR	NR	NR	60		
Simoni	2009	Brazil	NR	NR	NR	126		

Table 2: studies without complete patient refusal and participation information

Discussion

- Overall, 18% who were approached for methadone studies refused.
- Refusal rates were higher in the United States compared to countries in Europe or South America. (Figure 2)
- Only 9 of the 14 eligible randomized clinical trials reported patient refusal rates. Future trials should be transparent with their patient recruitment strategies.
- Our study highlights that effective patient education will be important for recruitment for future randomized controlled trials.
- Discussing perioperative methadone with patients, as part of an informed consent or as part of general practice, can help change inaccurate and negative perceptions of the medication.

Works Cited

- Murphy GS, Avram MJ, Greenberg SB, et al. Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients: A Randomized, Double-blind, Placebo-controlled Trial. Anesthesiology. 2021;134(5):697-708.2.
- Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative Methadone for the Prevention of Postoperative Pain: A Randomized, Double-blinded Clinical Trial in Cardiac Surgical Patients. Anesthesiology. 2015;122(5):1112-1122.3.
- Salsitz E, Wiegand T. Pharmacotherapy of Opioid Addiction: "Putting a Real Face on a False Demon". J Med Toxicol. 2016;12(1):58-63