

Statewide Ketamine and Esketamine Prescribing Trends in Rhode Island, 2017–2023

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ABSTRACT

Ketamine is a versatile anesthetic that has been widely used off-label to treat a variety of indications. Esketamine, a derivative of ketamine, is FDA-approved to treat treatment-resistant depression. This report compares statewide prescription ketamine and esketamine trends. Using PDMP data from 2017–2023, prescription and prescriber characteristics, and patient demographics were compared between esketamine and ketamine prescriptions. During this time, ketamine prescriptions, patients, and providers rose 55.8%, 30.6%, and 2.8% since 2017. Esketamine prescriptions increased 1289.4% since 2019. In 2023, ketamine prescriptions were primarily in powder form (98.7%) and paid for out-of-pocket (83.9%), whereas esketamine prescriptions were primarily paid for by insurance (80.2%). The proportion of ketamine prescribed in RI but dispensed out-of-state have increased 22% since 2022 (18% of total dispensations). As more people seek treatment for mental health disorders, ketamine and esketamine prescriptions continue to rise. Understanding ketamine and esketamine use can help mitigate associated adverse events.

KEYWORDS: Ketamine, Esketamine, Rhode Island, Off-label, Psychiatric Disorders

INTRODUCTION

Ketamine, a dissociative anesthetic, was first synthesized and introduced to the medical community in the 1960s with Food and Drug Administration (FDA) approval as an intravenous anesthetic in 1970.^{1,2} In 1999, ketamine became a Schedule III non-narcotic substance under the Controlled Substance Act (CSA). Ketamine is a versatile drug; it demonstrates both anesthetic and analgesic properties and depending on the dose, can also have dissociative effects, such as feeling detached from one's body, hallucinations, and changes in thoughts, emotions, and consciousness. Despite FDA approval only for induction and maintenance of general anesthesia, ketamine is widely used off-label to treat a range of medical and mental health conditions. For example, ketamine has been used via intravenous and intramuscular routes in clinical practice in the hospital acute care setting

for acute pain management, treatment of severe agitation, procedural sedation, and refractory seizures.³ Studies investigating ketamine's use for the treatment of psychiatric conditions began in the 1990s but it wasn't until 2019, when intranasal esketamine (Spravato®), a ketamine derivative, was FDA-approved as a therapy for treatment-resistant depression. The drug may only be administered in healthcare settings certified in the Spravato® Risk Evaluation and Mitigation Strategy (REMS) program.⁴ Due to concerns for sedation, dissociation, and other toxicities, the Spravato® REMS program requires that patients be monitored by a healthcare provider for two hours after administration. The program collects data on patient demographics and psychiatric history, dosing, and side effects after each dose administered. Over the last decade, a growing number of health care practitioners across a variety of specialties have started to prescribe and/or dispense subanesthetic regimens of ketamine off-label for the treatment of depression, post-traumatic stress disorder, anxiety, and other psychiatric disorders.^{2,5}

Although some ketamine treatment for psychiatric illness is provided via integrated interventional psychiatry programs, freestanding clinics administering ketamine outside of comprehensive health care systems have proliferated in recent years, providing intravenous and non-parenteral formulations via compounding pharmacies.⁶ As the drug is prescribed off-label, there are no requirements for certification of providers/clinics or data monitoring as with the Spravato® REMS program. Many commercial insurance plans do not cover ketamine treatment but will cover esketamine treatment. Extensive media coverage has promoted the potential benefits of ketamine as a mental health therapeutic to the public.⁷ Further, during the COVID-19 pandemic there was an influx of telehealth providers that used the increased regulatory flexibility around controlled substance prescribing via telehealth for ketamine prescribing for psychiatric treatment. Though its safety profile is well established as an analgesic and anesthetic in a clinician-monitored health care setting, much is still unknown about the safety and efficacy of using ketamine for mental health conditions and long-term consequences of chronic ketamine use. Few studies have explored prescription ketamine trends overall, and even fewer during the surge of mental health illness during and after the COVID-19 pandemic.⁸ The aim of this report is to characterize the landscape of ketamine and esketamine

prescribing both for FDA-approved indications and off-label use, including details on the patterns of prescribing and provider, pharmacy, and payment characteristics to provide insight into prescription ketamine and esketamine use trends in Rhode Island (RI).

MATERIAL AND METHODS

Data from the RI Prescription Drug Monitoring Program (PDMP) was used to identify ketamine and esketamine prescription records dispensed to RI residents from 2017–2023. Pharmacies operating in and prescriptions dispensed from RI, Massachusetts (MA), and Connecticut (CT) were not considered out-of-state as they border RI. Esketamine and ketamine products found in the PDMP do not represent all products administered in RI as these substances may be administered in the outpatient clinical care setting and bypass pharmacy dispensation.

Product quantity is a variable that reflects the total grams of powder used for the entire prescription. Compounded prescriptions have reportable formulations taken from the National Drug Code (NDC) associated with the product. A

product with an NDC associated with a powder formulation can be made into other formulations (troche, tablet, etc.) by a compounding pharmacy, but the reportable formulation will remain as a powder. NDCs of prescribed ketamine and esketamine are listed in **Box 1**.

A unique patient identification variable was created for each patient who had a prescription dispensed over the study period using the patient's first name, last name, and date of birth. An identification variable was also created for prescribers, using their first name, last name, and Drug Enforcement Administration (DEA) number. The number of ketamine and esketamine prescriptions per 1,000 people is displayed by region, which were pre-determined and match those used in RI Department of Health non-fatal drug overdose surveillance.⁹ To determine the number of prescriptions per 1,000 people per region, the total prescriptions dispensed to residents of each region were divided by the regional population and multiplied by 1,000. The year-to-year RI population, as well as regional population, has remained stable over the study timeframe.

Statistical analysis was conducted using SAS 9.4 (Cary, NC). To detect significant associations between outcomes and time, we conducted spearman's rank correlation tests. Significant associations were defined as having a p-value of <0.05. Only significant associations were reported.

Box 1. National Drug Codes (NDCs) of ketamine and esketamine prescriptions included in this analysis.

Ketamine	
143950810	51552069702
143950901	51552069704
143950910	51552069705
395807043	51552069706
409205105	51552069707
409205115	51927279000
409205310	52372088502
38779175400	52372088504
38779175404	52372088505
38779175405	60592040101
38779175407	62991108701
38779175408	62991108702
38779175409	62991108704
42023011310	62991108705
42023011410	62991108707
42023011510	63275998004
42023013910	63275998005
49452391202	63275998009
49452391203	67457000110
49452391207	67457018120
82393011610	82393011611
Esketamine	
50458002802	50458002803

RESULTS

From 2017–2023, there were 5,133 ketamine prescriptions dispensed to RI residents, increasing 55.8% from 699 in 2017 to 1,089 in 2023 (**Table 1**). From 2019–2023, there were 3,294 esketamine prescriptions dispensed to RI residents, increasing 1,289.4% from 123 in 2019 to 1,709 in 2023 (**Table 2**). Both ketamine ($\rho=1.0$, $p<.0001$) and esketamine ($\rho=1.0$, $p<.0001$) showed a strong, positive trend from 2020–2023. Ketamine prescriptions were primarily reported in the PDMP in powder form, accounting for 98.7% of prescriptions in 2023 (**Table 1**). Most ketamine prescriptions were paid out-of-pocket and increased from 77.5% in 2017 to 83.9% in 2023 (**Table 1**). Esketamine prescriptions, however, were primarily paid by other means such as private and public insurance (**Table 2**). In 2017, 43.5% of ketamine prescriptions contained a total quantity of 10–50g of ketamine, but by 2023, 10–50g range accounted for only 8.4% of dispensed ketamine prescriptions and most (47.3%) ketamine prescriptions were smaller, containing a total of <1–2g of ketamine (**Table 1**). All esketamine prescriptions contained ≤ 9 g of product throughout the study period (**Table 2**). In 2017, nearly 1/3 of ketamine prescriptions consisted of a 1-to-10-day supply, and 1/3 of prescriptions had a 30+ day supply. In 2023, 53.1% of ketamine prescriptions had a 30+ day supply (**Table 1**). The majority of esketamine prescriptions consisted of a 1–10-day supply throughout the study period (**Table 2**).

Table 1. Ketamine prescription characteristics, prescriber and dispenser characteristics, and patient demographics in Rhode Island, 2017–2023.

	2017	2018	2019	2020	2021	2022	2023
Prescription characteristics							
Prescriptions dispensed	699	634	650	629	666	766	1,089
Formulation Type							
Powder	508 (72.7%)	503 (79.3%)	535 (82.3%)	532 (84.6%)	538 (80.8%)	706 (92.2%)	1,078 (98.7%)
Other/Missing	191 (27.3%)	131 (20.6%)	115 (17.6%)	97 (15.4%)	128 (19.2%)	60 (7.8%)	11 (1.1%)
Quantity (g)							
<1–2	166 (23.8%)	219 (34.5%)	294 (45.3%)	274 (43.6%)	254 (38.1%)	257 (33.6%)	517 (47.3%)
3–9	148 (21.2%)	147 (23.2%)	170 (26.2%)	185 (29.4%)	215 (32.3%)	215 (28.1%)	268 (24.5%)
10–50	304 (43.5%)	216 (34.1%)	136 (20.9%)	105 (16.7%)	160 (24.0%)	170 (22.2%)	92 (8.4%)
51+	57 (8.2%)	38 (6.0%)	30 (4.6%)	36 (5.7%)	10 (1.5%)	23 (3.0%)	13 (1.2%)
Days' Supply							
1–10	247 (35.3%)	217 (34.2%)	226 (34.8%)	133 (21.1%)	189 (28.4%)	196 (25.6%)	163 (14.9%)
11–20	146 (20.9%)	153 (24.1%)	159 (24.5%)	219 (34.8%)	151 (22.7%)	178 (23.2%)	233 (21.3%)
21–29	80 (11.4%)	72 (11.4%)	84 (12.9%)	90 (14.3%)	109 (16.4%)	102 (13.3%)	116 (10.6%)
30+	226 (32.3%)	192 (30.3%)	181 (27.9%)	187 (29.7%)	217 (32.6%)	290 (37.9%)	580 (53.1%)
Out-of-Pocket Payment	542 (77.5%)	500 (73.8%)	512 (78.8%)	496 (78.9%)	578 (86.8%)	643 (83.9%)	643 (83.9%)
Prescriptions dispensed out-of-state	101 (17.5%)	66 (13.4%)	51 (9.7%)	69 (14.0%)	44 (8.9%)	95 (16.0%)	514 (52.0%)
Prescriptions dispensed in compound pharmacies	633 (90.6%)	575 (90.7%)	605 (93.1%)	573 (91.1%)	624 (93.7%)	711 (92.8%)	1,098 (99.1%)
Prescriber/Pharmacy Characteristics							
Prescribers	105	97	95	89	99	107	108
Pharmacies	29	26	23	24	19	26	26
Out-of-state	9	9	12	10	7	13	16
Compounding	22	21	19	19	16	24	22
Patient Demographics							
Patients dispensed ketamine	222	227	173	143	153	162	290
Median number of prescriptions per person [IQR]	2.0 [1.0,3.0]	1.0 [1.0,4.0]	2.0 [1.0,4.0]	2.0 [1.0,5.0]	2.0 [1.0,5.0]	2.0 [1.0,6.0]	2.0 [1.0,4.0]
Median age in years [IQR]	58.0 [48.0,67.0]	57.0 [47.0,68.0]	54.0 [45.0,69.0]	54.0 [39.0,66.0]	55.0 [41.0,67.0]	52.0 [38.0,62.0]	46.0 [36.0,58.0]
Sex at birth							
Female	147 (66.2%)	143 (63.0%)	103 (59.5%)	81 (56.6%)	96 (62.8%)	97 (59.9%)	171 (59.0%)
Male	73 (32.9%)	81 (35.7%)	65 (37.6%)	60 (42.0%)	56 (36.6%)	59 (36.4%)	109 (37.6%)

The number of ketamine prescribers remained relatively stable over time and prescribers showed a strong, positive trend from 2020-2023 ($\rho=1.0$, $p<.0001$; **Table 1**, **Figure 1**). The number of unique esketamine prescribers remains under 20 for each year, increasing 116.7% from six in 2019 to 13 in 2023 (**Table 2**). A total of 67 different pharmacies filled ketamine prescriptions during the study period, with 54 (80.6%) being compound pharmacies. Each year >90% of ketamine prescriptions are dispensed from a compound pharmacy (**Table 1**). In contrast, there were only nine pharmacies filling esketamine prescriptions from 2019–2023,

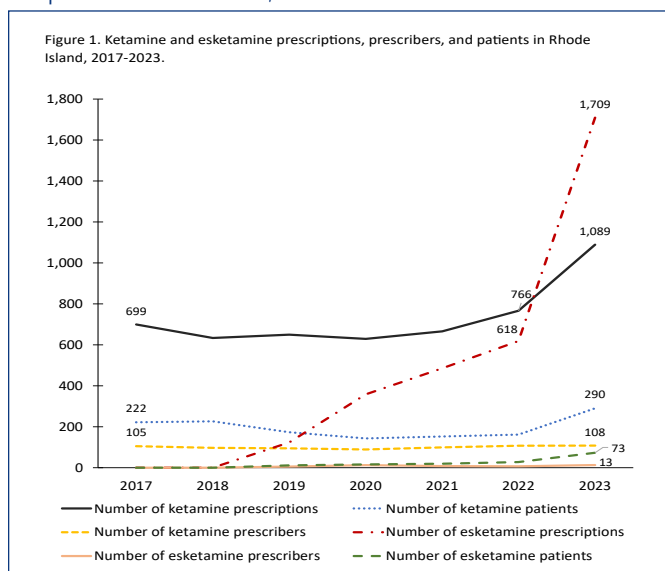
and 88.9% of them were compound pharmacies (**Table 2**). Each year, nearly all (>99%) of esketamine prescriptions were dispensed from a compound pharmacy (**Table 2**). From 2017-2023, over 900 ketamine prescriptions were dispensed out-of-state. The proportion of ketamine prescriptions dispensed from out-of-state pharmacies increased 197.1%, from 17.5% in 2017 to 52.0% in 2023 (**Table 1**). Out-of-state esketamine prescriptions remained close to zero throughout the study timeframe. (**Table 2**).

The number of patients dispensed ketamine prescriptions increased 30.6% from 222 in 2017 to 290 in 2023. This is

Table 2. Esketamine prescription characteristics, prescriber and dispenser characteristics, and patient demographics in Rhode Island, 2017–2023.

	2019	2020	2021	2022	2023
Prescription Characteristics					
Prescriptions dispensed	123	358	486	618	1709
Quantity (g)					
<1-2	42 (34.2%)	49 (13.7%)	36 (7.4%)	71 (11.5%)	63 (8.0%)
3-9	81 (65.9%)	309 (86.3%)	450 (92.6%)	547 (88.5%)	726 (92.0%)
Days' Supply					
1-10	123 (100%)	357 (99.7%)	486 (100%)	616 (99.7%)	789 (100%)
21-29	0	<5	0	0	0
30+	0	0	0	<5	0
Payment					
Out-of-Pocket	10 (8.1%)	28 (7.8%)	121 (24.9%)	267 (43.2%)	339 (19.8%)
Other	113 (91.9%)	330 (92.2%)	365 (75.1%)	351 (56.8%)	1370 (80.2%)
Prescriptions dispensed out-of-state	0	0	<5	0	0
Prescriptions dispensed in compound pharmacies	123 (100%)	358 (100%)	486 (100%)	618 (100%)	1,707 (99.9%)
Prescriber/Pharmacy Characteristics					
Prescribers	6	12	8	7	13
Pharmacies	<5	<5	<5	<5	<5
Out-of-state	0	0	<5	0	0
Compounding	<5	<5	<5	<5	<5
Patient Demographics					
Patients dispensed esketamine	11	16	20	28	73
Median number of prescriptions per person [IQR]	10 [7.0,15.0]	16.5 [5.5,40.5]	17.5 [9.5,37.5]	21.5 [4.0,37.0]	18.0 [12.0,30.0]
Median age in years [IQR]	48.0 [40.0,62.0]	50.0 [41.5,61.5]	52.5 [43.0,62.0]	53.0 [42.5, 61.0]	50.0 [37.0,62.0]
Sex at birth					
Female	<5 (27.3%)	9 (56.3%)	10 (50.0%)	15 (53.6%)	47 (64.4%)
Male	8 (72.7%)	7 (42.8%)	10 (50.0%)	13 (46.4%)	26 (35.6%)

Figure 1. Ketamine and esketamine prescriptions, prescribers, and patients in Rhode Island, 2017–2023.



largely accounted for by the steep increase in patients dispensed ketamine prescriptions in 2023, as there was a general decrease in the number of patients with ketamine prescriptions between 2019–2022 compared to earlier study years (Table 1, Figure 1). The number of ketamine patients showed a strong, positive trend from 2020-2023 ($p=1.0$, $p<.0001$). Each year, greater than 55% of recipients were female. The median age of patients receiving ketamine prescriptions in 2017 was 58 years old and 46 years old in 2023 (Table 1). The number of patients dispensed esketamine prescriptions increased 563.6% from 11 in 2019 to 73 in 2023 (Table 2). The number of esketamine patients showed a strong, positive trend from 2020-2023 ($p=1.0$, $p<.0001$). In total, females make up 58.4% of esketamine patients. The median age of patients receiving esketamine prescriptions was 48 years in 2019 and 50 years in 2023 (Table 2). The median number of ketamine prescriptions dispensed per person was two prescriptions each year, except for 2018, which was one prescription per person (Table 1). The median number of esketamine prescriptions per person each year was

Table 3. Ketamine and esketamine prescriptions dispensed per 1,000 people by Rhode Island region, 2017–2023.

Region #	Region	Number of ketamine prescriptions per 1,000 people	Number of esketamine prescriptions per 1,000 people
1	Burrillville, Foster, Gloucester, Scituate	11.7	0.97
2	Woonsocket	5.6	1.1
3	Cumberland, Lincoln, Smithfield, North Smithfield	6.6	3.5
4	Johnston, North Providence	5.4	6.7
5	Central Falls, Pawtucket	3.2	3.7
6	Providence	7.1	3.3
7	Cranston	5.1	6.5
8	Warwick, West Warwick, Coventry	4.1	3.3
9	Jamestown, Bristol, East Providence, Warren, Portsmouth, Tiverton, Little Compton, Middletown, Newport, Barrington	1.7	3.1
10	East Greenwich, West Greenwich, Exeter, Richmond, Hopkinton	7.0	6.0
11	Charlestown, North Kingstown, South Kingstown, Narragansett, Westerly, Block Island	6.3	2.1

higher than ketamine, increasing 80%, from 10 prescriptions per person in 2019 to 18 prescriptions per person in 2023 (Table 2).

The region with the highest rate of ketamine prescriptions per population was Burrillville, Foster, Gloucester, and Scituate (Region 1), with 11.7 prescriptions per 1,000 residents. The same region had a rate of 0.97 esketamine prescriptions per 1,000 residents. Providence (Region 6) and East Greenwich, West Greenwich, Exeter, Richmond, and Hopkinton (Region 10) have the next highest proportion of residents dispensing ketamine prescriptions at 7.1 of 1,000 people and 7.0 of 1,000, respectively (Table 3).

DISCUSSION

While there are studies and testimonials supporting the off-label use of ketamine for treatment-resistant depression and other psychiatric conditions, it is not approved by the FDA for these purposes. Despite its FDA approval and favorable safety profile, esketamine has only been dispensed 3,294 times in RI between 2019 and 2023. Ketamine prescription records listed in the RI PDMP are inherently prescribed off-label. When considering a prescription for ketamine for off-label indications, it is important for patients and providers to consider the absence of longitudinal follow-up data to determine safety and efficacy over time and concerns for bias in existing trials. Further, patients taking compounded drug products may not receive important information about risks as those products are not FDA approved and, thus, have not been evaluated for safety, efficacy, or quality or contain FDA-approved package insert.

While schedule II substances in RI can only be prescribed for 30 days at a time, ketamine and esketamine are schedule III drugs, so there is no statutory limit on days' supply dispensed.¹⁰ More than half of ketamine prescriptions dispensed

in RI in 2023 had a days' supply of 30 days or longer. While the average days' supply has increased, the per dose amount of ketamine appears to have decreased over time. Though more ketamine prescriptions are being dispensed, less concentrated ketamine prescriptions may reduce the risk of hypertension, overdose, and other severe side effects like hallucinations, agitation, psychosis, and loss of consciousness. According to the State Unintentional Drug Overdose Reporting System (SUDORS) and RI's Office of the State Medical Examiner (OSME) data, since 2015, there have been five fatal overdoses with ketamine as the cause of death in Rhode Island. Chronic ketamine use can raise risk for: 1) tolerance, the need for escalating doses; 2) physical and psychological dependence; 3) bladder dysfunction, ulcerative or interstitial cystitis, incontinence, abdominal cramping; 4) cognitive impairment.² Ketamine may also be prescribed as staggering doses, or once per week, making it challenging to conclude if prescribing trends allude to less concentrated doses. Esketamine has been consistently prescribed to RI residents as a ≤ 9 -day supply since 2019. This may be because esketamine (Spravato) must be administered in a clinic under supervision of healthcare provider. Additionally, the FDA recommends that esketamine be administered twice weekly during the induction phase and no more than once weekly during the maintenance phase.¹¹

Many ketamine prescriptions were filled in compound and/or out-of-state pharmacies. Nearly all esketamine prescriptions were dispensed by compound pharmacies. When esketamine is compounded, this allows clinicians to bypass REMS and prescribe the drug off-label. Though ketamine is relatively inexpensive, a series of ketamine infusion treatments for treatment-resistant depression costs roughly \$3,000 in RI.^{12,13} Because of the high cost, ketamine use is expected to be common among people of higher socio-economic status. However, in RI, we see low rates of prescription

use in towns such as Jamestown and Barrington (Region 9), which have both have high median household incomes. In contrast, esketamine is covered by many public and private third-party payers, which may explain why there are fewer esketamine prescriptions dispensed out-of-state. The rate of esketamine prescriptions per 1,000 people in Burrillville, Foster, Gloucester, Scituate (Region 1), and Woonsocket (Region 2), are low in comparison to the rate of ketamine prescriptions in these areas. In 2008, Woonsocket was designated a mental health professional shortage area, meaning that there were not enough mental health providers to cover the estimated population that requires mental health care.¹⁴ Burrillville, Foster, Gloucester, and Scituate are rural areas and typically have less access to general healthcare. In addition to these factors, esketamine utilization may be low due to the fact that these areas are of lower economic status and may not have insurance or may not have coverage under their existing insurance.¹⁵ Without insurance, a person might expect to pay \$240 for their esketamine prescription.¹⁶ Therefore, ketamine may be the more affordable option if paying out-of-pocket, even factoring in the cost-share of a physician office visit to receive the medication. While insurance coverage plays an important factor in the accessibility of esketamine, there are limited clinics that can administer the medication.

The use of data from the RI PDMP is a strength of this study, as it provides up to date data on substances dispensed from pharmacies in RI and includes data from pharmacies in 37 other states for RI residents. In addition to this, prescribers with a Controlled Substance Registration (CSR) in RI must have a physical practice location in the state where they can provide as needed treatment for patients. Although we are not able to determine if ketamine prescriptions are prescribed via telehealth, this requirement likely limited the impact of ketamine telehealth prescribing in RI when compared to other states. This work is subject to several limitations. The PDMP does not collect information on race or ethnicity, prescriptions prescribed but not dispensed, nor ketamine and esketamine prescriptions administered in clinics. The variability of the days' supply of a prescription a patient receives may depend on factors not fully captured by the PDMP such as: the condition being treated, treatment phase, and the patient's response to treatment. Days' supply data are either calculated or manually entered by the pharmacist, often to meet insurance requirements and may differ from actual use. The PDMP does not include data on a patient's dosing schedule. Because of this, it is difficult to compare the quantities in **Tables 1 and 2** to dosing recommendations provided by the FDA.^{11,17} ICD-10 codes are also not required to be entered by prescribing clinicians nor pharmacists into the PDMP.

If off-label ketamine or esketamine use is being considered, clinicians should weigh the risks and benefits and discuss them with their patients. Patients taking ketamine

and esketamine for off-label indications should be monitored and follow-up communications should be frequent. Future studies should focus on factors that lead people to seek and clinicians to prescribe ketamine treatment versus esketamine treatment for depression. As the number of ketamine and esketamine prescriptions increases, dispensing surveillance should continue, as well as efforts to educate the public and clinicians to foster responsible prescribing. Stakeholders should collaborate with prescribers and clinic owners, as well as legacy and social media outlets, to ensure that messaging and advertising are accurate and promote patient safety.

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