

Comparative safety of prescribed Esketamine and ketamine in relation to renal and urinary disorders: A pharmacovigilance perspective

S. Chiappini^a, A. Guirguis^{b,*}, N. Schifano^{c,d}, J.M. Corkery^e, F. Semeraro^f, A. Mosca^f,
G. D'Andrea^f, G. Duccio Papanti^{e,g}, D. Arillotta^{e,h}, G. Floresta^{e,i}, G. Martinotti^{e,f}, F. Schifano^e

^a UniCamillus University of Medical Sciences, Via di S. Alessandro 8, Rome, Italy

^b Pharmacy, Swansea University Medical School, The Grove, Swansea University, SA2 8PP, Swansea, Wales, UK

^c Department of Urology, ASST Sette Laghi, Varese, Italy

^d Circolo & Fondazione Macchi Hospital; University of Insubria, Varese, Italy

^e Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, AL10 9AB Hertfordshire, UK

^f Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, 66100 Chieti, Italy

^g Tolmezzo Community Mental Health Centre, ASUFC Mental Health and Addiction Department, via Bonanni 2, 33028 Tolmezzo, UD, Italy

^h Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, University of Florence, Viale G. Pieraccini, 6, 50139 Florence, Italy

ⁱ Department of Drug and Health Sciences, University of Catania, Catania, Italy

ARTICLE INFO

Keywords:

Esketamine

Ketamine

Urological safety

Pharmacovigilance

ABSTRACT

Intranasal esketamine, approved with oral antidepressants for adults with treatment-resistant depression (TRD), is the S-enantiomer of ketamine and has higher potency and affinity for N-Methyl-D-Aspartate receptors. Administered intranasally, it offers rapid absorption and onset, essential for severe depressive symptoms or suicidal impulses. Comparative studies on esketamine and ketamine's urological safety profiles show esketamine has lower or comparable risks of renal and urinary disorders. Ketamine, however, has documented cases of nephrotoxicity and severe urological issues in recreational users.

The study aims to further evaluate and compare these profiles against other antidepressants and antipsychotics using the Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS) data. ADR cases were reported to the FDA up to May 12, 2024, being drugs listed including esketamine, ketamine, quetiapine, aripiprazole, olanzapine, risperidone, citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine, amitriptyline, and clomipramine.

Risperidone showed the highest ADRs (107,418) and serious cases (71,515), with significant renal and urinary disorders reported, including acute kidney injury and urinary incontinence. Olanzapine, quetiapine, and aripiprazole also had high serious ADRs. Venlafaxine and fluoxetine were notable among antidepressants for acute kidney injury. Esketamine and ketamine were associated with lower urinary tract symptoms and nephrolithiasis. Disproportionality analysis revealed ketamine had higher odds of renal and urinary disorders compared to other drug classes, while esketamine had lower or comparable odds.

The data suggest a relatively favorable tolerability profile for these drugs, especially esketamine. However, the results highlight the necessity for more extensive studies to evaluate long-term safety and optimize treatment protocols.

* Corresponding author.

E-mail addresses: amira.guirguis@swansea.ac.uk (A. Guirguis), j.corkery@herts.ac.uk (J.M. Corkery), giuseppe.floresta@unict.it (G. Floresta), f.schifano@herts.ac.uk (F. Schifano).

<https://doi.org/10.1016/j.pnpbp.2024.111213>

Received 8 August 2024; Received in revised form 18 November 2024; Accepted 1 December 2024

Available online 6 December 2024

0278-5846/© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

1. Introduction

1.1. Intranasal esketamine: approval, indications, mechanism of action, dosing regimen

Intranasal esketamine received approval from the Food and Drug Administration (FDA) in March 2019 and from the European Medicines Agency (EMA) later that year, marking a significant milestone in the treatment of specific psychiatric conditions. Specifically, the FDA approval was for two distinct indications: treatment-resistant depression (TRD) and major depressive disorder with suicidal ideation (MDSI). For TRD, esketamine is prescribed in conjunction with a newly initiated oral antidepressant, typically a selective serotonin reuptake inhibitor (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Conversely, for MDSI, esketamine is used as an adjunct to standard-of-care (SoC) treatments, which may include antipsychotics such as quetiapine, olanzapine, or aripiprazole, in addition to antidepressants (FDA, 2019). Unlike FDA approvals, the EMA indication does not explicitly include treatment for MDSI. However, real-world clinical use often involves diverse treatment regimens, which may include antipsychotics for adjunctive management. These differences in treatment protocols and concomitant medication regimens necessitate careful evaluation of safety profiles, as the co-prescribed medications may contribute to or mitigate adverse effects observed in clinical and post-marketing settings. This approval was strongly supported by the results of pivotal Phase 3 trials, which demonstrated that esketamine could significantly reduce the symptoms of depression and also reduce the risk of relapse in these patients (Daly et al., 2019).

Chemically, esketamine is the S-enantiomer of ketamine, which is a racemic mixture of two mirror image molecules, the (S+)-ketamine (esketamine) and the (R-)-ketamine (arketamine). The two enantiomers share pharmacokinetic properties but exhibit distinctly different pharmacodynamic characteristics. Notably, esketamine has a greater affinity and four times the potency of the R-enantiomer for the N-methyl-D-aspartate (NMDA) receptors. This higher potency at NMDA receptors underpins its primary mechanism of action as a non-selective, non-competitive antagonist of these receptors (Boudieu et al., 2023). By inhibiting NMDA receptors, esketamine induces a transient increase in the release of glutamate, which then enhances the stimulation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This stimulation is crucial for augmenting neurotrophic signalling pathways that involve brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR), potentially facilitating the restoration and enhancement of synaptic functions in critical brain areas associated with mood regulation and emotional behaviour (Salahudeen et al., 2020). The BDNF plays a critical role in synaptic plasticity, neuronal survival, and the modulation of pain pathways. Recent evidence also suggests that BDNF may contribute to the pathogenesis of neurogenic bladder dysfunction by influencing sensory and motor neural pathways involved in bladder control. Given that ketamine and esketamine have been shown to modulate BDNF levels, it is plausible that dysregulation of BDNF could play a role in the neurological genesis of bladder problems associated with these agents. However, this hypothesis remains largely unexplored in the context of urological safety (Frias et al., 2015).

The capacity of esketamine to influence both glutamatergic and gamma-amino-butyric acid (GABA)ergic systems not only highlights its role as an effective rapid-acting antidepressant but also suggests its potential utility as a mood stabilizer, particularly for the treatment of bipolar disorder with mixed features, including anxiety and dysphoria. This broad pharmacodynamic profile underscores esketamine potential to stabilize mood fluctuations without the high risk of inducing manic episodes, which is a critical consideration in the pharmacotherapy of bipolar disorders (D'Andrea et al., 2023a; D'Andrea et al., 2023b). Administered intranasally, esketamine offers the advantage of rapid absorption and onset of action, which is critical for patients experiencing

severe depressive symptoms or acute suicidal impulses. The method of administration provides higher bioavailability than oral forms and allows for the quick establishment of therapeutic drug levels in the system, making it an essential option for rapid intervention in critical care setting (Bahr et al., 2019). The specific dosing regimen has been meticulously designed to optimize both efficacy and safety; its administration involves a structured dosing schedule that begins with an induction phase, which lasts for four weeks. During this initial phase, patients are administered 56 mg on the first day, followed by either 56 mg or 84 mg twice weekly. This frequent dosing is intended to rapidly establish and stabilize esketamine levels in the body to quickly mitigate the acute symptoms of depression. Transitioning into the maintenance phase, the frequency of administration is reduced: from weeks five to eight, the dosing is adjusted to once weekly, maintaining the dose at either 56 mg or 84 mg, depending on clinical response and tolerability (Chiappini et al., 2023); beyond the eighth week, the dosing frequency may be further decreased to once every two weeks, although some patients may continue to require weekly doses. This dosing strategy not only tailors the treatment to individual patient needs over time but also minimizes exposure to the drug, thereby potentially reducing the risk of side effects and enhancing overall treatment sustainability; in fact, despite its therapeutic benefits, ongoing research is required to fully understand the long-term effects and safety profile of esketamine, particularly concerning its sustained use in the clinical setting.

1.2. Safety profiles of esketamine in randomized controlled trials

In the exploration of esketamine safety profile, its adverse effects were meticulously evaluated across numerous randomized controlled trials (RCTs) (Table 1). The TRANSFORM-1 trial, led by Fedgchin et al. (2019), investigated the safety of fixed doses of 56 mg and 84 mg of esketamine administered intranasally twice per week in adults aged 18 to 64. Common adverse effects reported were nausea (18 %), dizziness (15 %), dissociation (12 %), headache (10 %), and vertigo (5 %) (Fedgchin et al., 2019). Similarly, employing a flexible dosing regimen in a double-blind, multicenter setup, the TRANSFORM-2 study found results similar to those of TRANSFORM-1 in terms of the types of side effects observed, with additional reports of dysgeusia. Dissociation was observed in 17.7 % of patients, dizziness in 13.5 %, vertigo also in 13.5 %, and dysgeusia in 12.5 %. The safety evaluation was similarly rigorous, encompassing a suite of assessments designed to comprehensively monitor both physical and psychological side effects (Popova et al., 2019). The TRANSFORM-3 trial, conducted by Ochs-Ross et al. (2020), specifically targeted an older cohort, with participants aged 65 and above. This trial is particularly noteworthy as it highlighted potential age-related sensitivities, such as an increased incidence of transient elevations in blood pressure (10 %) and fatigue (8 %) (Ochs-Ross et al., 2020). Further extending the scope of safety assessment, the SUSTAIN-1 (Daly et al., 2019) and SUSTAIN-2 trials (Wajs et al., 2020) focused on the maintenance phase of esketamine treatment: SUSTAIN-1 demonstrated that esketamine nasal spray plus an oral antidepressant significantly delayed relapse in patients with TRD. Common adverse effects included dizziness (27.6 %), dissociation (26.3 %), nausea (21.1 %), and headache (20.1 %). In SUSTAIN-2, 90.1 % of participants experienced treatment-emergent adverse events (TEAEs), the most frequent being dizziness (32.9 %), dissociation (27.6 %), nausea (25.1 %), and headache (24.9 %). Importantly, 17 % of participants reported TEAEs related to renal and urinary disorders, such as pyelonephritis, urinary tract infections (UTIs), and cystitis. Most urinary-related TEAEs were mild-to-moderate and resolved within two weeks. There were five cases of cystitis that resolved whilst continuing esketamine treatment. Notably, no renal or urinary TEAEs led to discontinuation of treatment, although some cases required dose adjustment or temporary interruption. This contrasted with the findings in SUSTAIN-1 and SUSTAIN-3, where no urinary system-related side effects were reported. In the REAL-ESK study, most patients experienced at least one side effect, with

Table 1
Adverse Effects including Renal/Urinary Adverse Effects recorded in Esketamine Clinical Trials.

Trial	Number of Participants	Esketamine Dosage and Regimen	Reported Adverse Effects	Renal/Urinary Adverse Effects
TRANSFORM-1 (2019)	346	56 mg or 84 mg, twice weekly for 4 weeks	Nausea (18 %), dizziness (15 %), dissociation (12 %), headache (10 %), vertigo (5 %)	None
TRANSFORM-2 (2019)	227	56 mg or 84 mg, flexible dosing, twice weekly for 4 weeks	Dissociation (17.7 %), dizziness (13.5 %), vertigo (13.5 %), dysgeusia (12.5 %)	None
TRANSFORM-3 (2020)	137	28 mg, 56 mg, or 84 mg, twice weekly for 4 weeks	Vertigo (20.8 % SPRAVATO+AD vs 7.7 % AD+PBO), nausea (18.1 % vs 4.6 %), increased blood pressure (12.5 % vs 4.6 %), fatigue (12.5 % vs 7.7 %), headache (12.5 % vs 3.1 %), dissociation (12.5 % vs 1.5 %)	None
SUSTAIN-1 (2019)	297	56 mg or 84 mg, flexible dosing for maintenance phase	Dissociation (27 %), dizziness (26 %), nausea (25 %), dysgeusia (20 %), somnolence (20 %), headache (24 %)	None
SUSTAIN-2 (2020)	802	28 mg, 56 mg, or 84 mg, flexible dosing for long-term safety	<u>Induction Phase</u> (N = 624): Dizziness (30.8 %), dissociation (24.0 %), nausea (22.9 %), headache (20.2 %), somnolence (12.3 %), hypoaesthesia (11.5 %); <u>Optimization/Maintenance Phase</u> (N = 477): Headache (21.2 %), dizziness (22.0 %), nausea (15.3 %), dissociation (19.3 %), viral upper respiratory tract infection (10.7 %), vomiting (8.2 %)	136 patients (17.0 %) reported TEAEs related to renal and urinary disorders, including UTI (8.1 %), cystitis, pyelonephritis, and others. Most cases were mild-to-moderate and resolved within 2 weeks
REAL-ESK (2022)	116	56 mg or 84 mg, flexible dosing for induction and maintenance	Dissociative symptoms (39.7 %), sedation (28.4 %), transient hypertension (10.3 %), severe psychomotor agitation (1.7 %), manic symptoms (2.6 %), anxiety (2.6 %), headache (2.6 %), no side effects (27.6 %)	None
SUSTAIN-3 (2023)	1148	56 mg or 84 mg, flexible dosing for induction and maintenance	<u>Induction Phase</u> (N = 458): Dissociation (21.8 %), dizziness (20.5 %), nausea (17.7 %), vertigo (16.8 %), dysgeusia (16.6 %), headache (15.1 %); <u>Optimization/Maintenance Phase</u> (N = 1110): Headache (33.2 %), dizziness (30.8 %), nausea (29.9 %), dissociation (23.2 %), nasopharyngitis (22.6 %), and somnolence (22.2 %)	None

Abbreviations: AD: antidepressant; PBO: placebo; TEAE: treatment-emergent adverse events; UTI: urinary tract infection.

dissociative symptoms reported by 39.7 % of patients, sedation by 28.4 %, and transient hypertension by 10.3 %. Noteworthy, there was a relatively low occurrence of more severe side effects such as manic symptoms and psychomotor agitation, reported at rates of 2.6 % and 1.7 %, respectively. Importantly, only 2.58 % of patients discontinued treatment due to adverse effects at the one-month follow-up, highlighting esketamine manageability even outside the framework of controlled trials’ settings (Martinotti et al., 2022). Finally, the SUSTAIN-3 study offered comprehensive insights into the safety of esketamine nasal spray in a cohort of patients who underwent a second induction period. During both the induction (IND) and optimization/maintenance (OP/M) phases, a significant proportion of participants reported treatment-emergent adverse events (TEAEs), with 58.3 % during IND and 83.3 % during OP/M experiencing at least one TEAE. Most frequently encountered TEAEs during the IND phase included dissociation, dizziness, and dysgeusia. In the OP/M phase, the profile of adverse events expanded to include headache, somnolence, and nausea among the most common (Castro et al., 2023). In none of these clinical trials, with the exception of the SUSTAIN-2, there were any side effects related to the urinary system; however, the comprehensive safety data garnered from these trials underscore the essential role of ongoing pharmacovigilance on esketamine after receiving FDA and EMA approval. This enduring oversight ensures that the use of esketamine remains not only effective but also safe across various patient groups, highlighting the importance of adapting and refining clinical practices based on real-world experiences.

1.3. Urothelial toxicity associated with the use of ketamine and esketamine

While the benefits of ketamine and esketamine for TRD are well documented, their potential side effects, and with a specific focus on urinary system, are described very well for ketamine, but not for esketamine (Tables 1 and 2). From a biological point of view, the

primary pathway of ketamine urothelial injury involves direct toxicity to the bladder’s epithelial cells (Baker et al., 2016; Findeis et al., 2020a). This is thought to be mediated by ketamine’s metabolites, which induce oxidative stress and apoptotic pathways within these cells. Notably, esketamine shares this metabolite pathway, but has shown a reduced incidence of urothelial toxicity compared to ketamine, suggesting differences in either metabolite dynamics or receptor interactions (Baker et al., 2016). Treating 25 patients up to three times weekly with esketamine at doses ranging from 0.25 to 0.5 mg/kg, Findeis et al. found a significant improvement in the depression scores and no significant trends toward an increase in urinary toxicity markers, including leukocytes, erythrocytes, proteins, and free hemoglobin throughout the treatment course, suggesting that the use of esketamine, whether in single or repeated doses, is unlikely to induce urothelial toxicity (Findeis et al., 2020a). In contrast, the broader use of ketamine, particularly outside controlled environments, presents with substantial risks. A pharmacovigilance study from Schifano et al. scrutinizes the incidence of ketamine-induced uropathy (KIU); The study identified 11,632 reports of adverse drug reactions (ADRs) related to ketamine, with 17.7 % of these reports implicating urological issues. Notably, a significant portion of these ADRs occurred within the first year of ketamine administration, emphasizing the potential acute and subacute urological risks associated with its use (Schifano et al., 2021). Consistently, a case report by Bruculeri et al. documented the acute nephrotoxic effects of ketamine, which had been administered as a series of intravenous infusions to a patient with a history of significant pain issues who developed acute interstitial nephritis, necessitating immediate renal intervention and dialysis (Bruculeri et al., 2023).

Conversely, Shahani et al. explored the severe urological consequences of ketamine recreational use, documenting a series of nine patients suffering from ketamine-associated ulcerative cystitis. This study detailed the clinical journey of patients presenting with symptoms such as dysuria, frequency, urgency, and gross hematuria, none of whom had infections as per sterile urine cultures. Advanced diagnostic techniques

Table 2

Adverse Effects including Renal/Urinary Adverse Effects recorded in Ketamine-related literature (trial/case reports).

Trial or case report	Number of participants	Ketamine Dosage and Regimen	Reported Adverse Effects	Renal/Urinary Adverse Effects
Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression (Loo et al., 2016) NCT01582945	15	Dose titration starting at 0.1 mg/kg, increasing by 0.1 mg/kg up to 0.5 mg/kg, administered via IV, IM, and SC routes, each treatment separated by ≥ 1 week, with one placebo control treatment randomly inserted	Dissociation (30 %), dizziness (20 %), increased heart rate (15 %), increased blood pressure (10 %)	No significant renal/urinary adverse effects reported
Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial (Grunebaum et al., 2017) NCT02094898	80	Single dose of 0.5 mg/kg ketamine given intravenously over 40 min	Dissociation (27 %), dizziness (28 %), nausea (25 %), headache (22 %), dysgeusia (20 %)	No significant renal/urinary adverse effects reported
At-home, sublingual ketamine telehealth for moderate to severe anxiety and depression (Hull et al., 2022) NCT04234533	1247	300–450 mg sublingual ketamine tablets administered at home with telehealth support, over 4 weeks	Side effects (4.7 % after session 2, 3.8 % after session 4), dissociation (82.9 % after session 2, 87.3 % after session 4), elevated heart rate, worsening depression, increased urinary pressure, hematuria, anxiety	Increased urinary pressure, hematuria (1 case)
Ketamine for Treatment-Resistant Depression (Anand et al., 2023) NCT02417064	403	Ketamine infusion (0.5 mg/kg IV twice weekly for 3 weeks) vs. ECT (3 times weekly for 3 weeks)	Dissociation (29 %), dizziness (20 %), headache (15 %), nausea (13 %), increased blood pressure (10 %)	None significant
Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression (Ekstrand et al., 2022) NCT02969417	186	Racemic ketamine (0.5 mg/kg IV thrice-weekly) vs. ECT (up to 12 sessions until remission)	Dissociative symptoms (59.8 %), anxiety (43.2 %), dizziness (67.4 %), headache (22.2 %), nausea (26.1 %)	Increased urinary frequency (1 %)
Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital (Wilkinson et al., 2019) NCT02659324	54	0.5 mg/kg IV over 40 min, initially single or double infusion protocol, later transitioned to a 4-infusion protocol over two weeks	Dissociation (40.7 %), elevated blood pressure (20.4 %), mild nausea (11.1 %)	None significant
Single and Repeated Ketamine Infusions for Reduction of Suicidal Ideation (Phillips et al., 2020) NCT02507219	37	0.5 mg/kg IV, 3 times a week for 2 weeks, followed by 1 time a week for 4 weeks	Cardiorespiratory effects (15 %), dissociation (20 %), dizziness (10 %)	None reported
Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression (Rot et al., 2010) NCT00548964	33	0.5 mg/kg IV, 6 infusions over 12 days	Increased blood pressure (20 %), dissociation (25 %), nausea (15 %)	None reported
Ketamine Augmentation for Major Depressive Disorder and Suicidal Ideation (Sinyor et al., 2018) NCT01882431	41	0.5 mg/kg IV, 4 infusions over 8 days	Dissociation (20 %), dizziness (15 %), increased blood pressure (10 %)	None reported
Ketamine-Induced Acute Interstitial Nephritis (Bruccheri et al., 2023)	1	0.35 mg/kg IV, 8 infusions over 2 weeks	Acute kidney injury, maculopapular rash, peripheral eosinophilia, elevated blood pressure, lethargy	Acute interstitial nephritis, elevated BUN and creatinine levels, presence of urine eosinophils
Rapid neuroplasticity changes and response to intravenous ketamine: a randomized controlled trial in treatment-resistant depression (Kopelman et al., 2023) NCT03674671	98	0.5 mg/kg IV, single infusion	Dissociation (20 %), dizziness (15 %), nausea (10 %), increased blood pressure (15 %)	None reported

Abbreviations: BUN: Blood Urea Nitrogen; ECT: Electroconvulsive therapy; IM: Intramuscular; IV: intravenous; SC: Subcutaneous.

revealed marked bladder wall thickening and severe inflammation, with histopathological examinations showing epithelial denudation and eosinophilic inflammation (Yeh et al., 2021). Similarly, a retrospective assessment of the impact of street ketamine on the urological systems of 59 individuals presenting at two major hospitals in Hong Kong showed severe lower urinary tract symptoms (LUTS), such as urgency, dysuria, and in some cases painful hematuria, which notably, were not attributed to bacterial infections (Chu et al., 2008). Extensive diagnostic evaluations, including cystoscopies and biopsies, indicated changes akin to those observed in chronic interstitial cystitis, with some patients also showing significant renal impairment evidenced by hydronephrosis and, in a few instances, papillary necrosis, suggesting a potential progression to chronic kidney disease.

Aim of the study: Considered the limited knowledge on urological adverse effects associated with esketamine and ketamine, the aim of this study is to evaluate and, using a disproportionality analysis, compare the urological safety profiles of esketamine and ketamine with those of second-generation antipsychotics (SGAs, e.g., quetiapine, aripiprazole, olanzapine and risperidone), SSRIs (e.g., citalopram, escitalopram, paroxetine, fluoxetine, sertraline), SNRIs (e.g., duloxetine, venlafaxine),

and tricyclic antidepressants (TCAs, e.g., amitriptyline, clomipramine). By examining these data, we seek to provide a clearer understanding of the safety profiles of esketamine and ketamine, thereby informing clinical decisions and improving patient care.

2. Methodology

For this study, ADRs were extracted from the Food and Drug Administration Adverse Event Reporting System (FAERS) in March 2024, focusing on esketamine and ketamine. The selected preferred terms (PTs) related to renal and urinary disorders were chosen based on the MedDRA hierarchy. These terms included Acute Kidney Injury, Urinary Retention, Urinary Incontinence, Renal Failure, Renal Impairment, Dysuria, Incontinence, Pollakiuria, Renal Disorder, Urinary Hesitation, Nephrogenic Diabetes Insipidus, Polyuria, Chronic Kidney Disease, Hematuria, Oliguria, Proteinuria, Anuria, Micturition Urgency, Renal Tubular Necrosis, Nephropathy Toxic, Hydronephrosis, Bladder Dilatation, Renal Injury, Nephropathy, Nocturia, Micturition Disorder, Chromaturia, Pyelocaliectasis, Renal Pain, Renal Papillary Necrosis, Ureteric Stenosis, Azotaemia, Nephritis, Tubulointerstitial Nephritis,

Hypertonic Bladder, Urinary Tract Obstruction, Prerenal Failure, End Stage Renal Disease, Leukocyturia, Focal Segmental Glomerulosclerosis, Nephrotic Syndrome, Urine Odour Abnormal, Hemoglobinuria, Ureterocele, Ureteric Hemorrhage, Kidney Enlargement, Ketonuria, Postrenal Failure. The FAERS data was accessed from the FAERS Public Dashboard from their publicly-available website <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/6b5a135f-f451-45be-893d-20aaec34e28e/state/analysis> (accessed on March 31st, 2024).

2.1. Data extraction and preparation

The FAERS database was queried using standardized drug names to ensure consistency. Generic drug names were used, and drug salts were excluded to broaden the scope of included ADRs. Advanced text mining and natural language processing (NLP) techniques were applied to automatically identify and extract drug names from the free-text fields in the FAERS reports. Data cleaning and standardisation were conducted to correct misspellings, abbreviations, and variations in drug names, including brand names, to maintain consistency across the dataset.

2.2. Role codes and drug codification

Each drug entry in the FAERS database is assigned a role code indicating its role in the reported adverse event. This analysis focused on drugs assigned the role code PS (Primary Suspect), which denotes the drug most likely responsible for the reported ADR. Information on drugs administered concurrently but not directly implicated in the ADRs was also included (assigned the concomitant role code). This approach allows for a nuanced analysis of the drugs associated with reported adverse events, considering their varying degrees of suspected involvement.

2.3. Comparative analysis

The analysis also included SGAs, SSRIs, SNRIs and TCAs for comparative purposes. Selected PTs related to renal and urinary disorders for these drug classes were identified using the same methodology. This comparative analysis aimed to contextualise the findings related to the total cases of esketamine and ketamine by evaluating the incidence of similar ADRs with these traditional psychotropic medications.

2.4. Disproportionality analysis

Analyses of descriptive data and pharmacovigilance disproportionality for renal and urinary disorder-related ADRs were conducted, with particular emphasis on ‘total cases’ of ADRs involving renal and urinary disorders. The descriptive analysis covered aspects such as sociodemographic details, country of origin, indication for use, co-use of other legal or illegal drugs, the identity of the ADR reporters, the number of cases annually and per reaction type, and the resulting outcomes (e.g., death, hospitalisation, or disability) for the selected drugs investigated. The EudraVigilance data analysis system (EVDAS) employed the frequentist reporting odds ratio (ROR) as the pharmacovigilance measure (Bihan et al., 2020). The odds ratio (OR) was used to determine the relationship between drug exposure and ADRs, indicating the probability of an ADR occurring under drug exposure compared to the probability of the ADR occurring without the drug exposure (Szumilas, 2010).

The formula for ROR is as follows:

ROR = $\frac{a/b}{c/d}$

(continued on next column)

(continued)

	Number of reports with event of interest	Number of reports without event of interest
	Number of reports with event of interest	Number of reports without event of interest
Ketamine or esketamine	a	b
Other drug classes (either SGAs, SSRIs, SNRIs or TCAs)	c	d

where:

- a = Number of reports with the event of interest for esketamine/ketamine
- b = Number of reports without the event of interest for esketamine/ketamine
- c = Number of reports with the event of interest for all other drug classes
- d = Number of reports without the event of interest for all other drug classes

Calculate the confidence Interval (CI) at 95 % = $e^{\text{LN(OR)} \pm 1.96 \cdot \text{SQRT}(1/a + 1/b + 1/c + 1/d)}$.

Calculate LN (OR).

Upper 95 % CI = $e^{\text{LN(OR)} + 1.96 \cdot \text{SQRT}(1/a + 1/b + 1/c + 1/d)}$.

Lower 95 % CI = $e^{\text{LN(OR)} - 1.96 \cdot \text{SQRT}(1/a + 1/b + 1/c + 1/d)}$ (Baker et al., 2016).

An elevated OR suggests a greater probability of renal and urinary disorder cases occurring when exposed to these selected drugs. On the other hand, an OR below 1 signifies a lower probability of these incidents happening with the drug. The CI for the OR is critical to evaluate. If the CI includes 1, it indicates that the OR lacks statistical significance (Prasad et al., 2008).

Data analyses were conducted using Microsoft Excel (version 97–2003).

2.5. Ethical considerations

As the data were reported anonymously, ethical approval was not required.

3. Results

ADR cases are summarized in Table 3, including information on total ADR cases reported to the FDA for various medications up to May 12, 2024, serious cases, specific renal and urinary disorders, and breakdowns of selected reactions for each drug. The drugs listed include esketamine, ketamine, quetiapine, aripiprazole, olanzapine, risperidone, citalopram, escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine, amitriptyline, and clomipramine.

Overall, taking in account absolute values, the analysis of the FAERS dataset revealed significant differences across drugs, with risperidone having the highest absolute number of ADRs (N = 107,418) and clomipramine the lowest (N = 2470). With regards to serious cases, risperidone, quetiapine, aripiprazole, and olanzapine showed the highest numbers (N = 71,515; 44,529; 52,582; and 64,011, respectively), indicating a substantial proportion of serious reactions associated to them. Specifically, considering renal and urinary disorders, aripiprazole, olanzapine, risperidone and quetiapine were associated with the highest absolute values (N = 2837; 4121; 3975; 2071, respectively), maintaining the same results when the unmasking analysis was carried out as well (N = 1092; 2122; 1392; 391, respectively).

Notable conditions include acute kidney injury, which was the most reported ADR, respectively with olanzapine (N = 784), risperidone (N =

Table 3

Summary of findings related to Renal and urinary adverse events recorded by the Food and Drug Administration (FDA) Adverse events reporting system (FAERS) collected up to May 12, 2024.

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
ESKETAMINE	7661	4714	156	140	LUTS (pollakiuria 29, micturition urgency 18, urinary incontinence 16, dysuria 5)	68	2011–2024
					Nephrolithiasis	16	
					Conditions involving the bladder (bladder pain 7, bladder disorder 6, interstitial cystitis 6)	19	
					Obstructive issues of the urinary tract (urinary retention)	19	
					Non-urollogic medical conditions (renal impairment 12, acute kidney injury 7, renal failure 5)	24	
KETAMINE	4739	4578	362	105	Nephrolithiasis	90	1998–2024
					Non-urollogic medical conditions (acute kidney injury 84, renal failure 15, renal infarct 13, oliguria 9, anuria 7, nephrogenic diabetes insipidus 5)	133	
					Urinary Tract Disorder	50	
					Haematuria	26	
					Obstructive issues of the urinary tract (hydronephrosis 26, urinary retention 18, ureteric stenosis 5)	49	
					LUTS (urinary incontinence 14, dysuria 13, lower urinary tract symptoms 8, pollakiuria 7)	42	
					Conditions involving the bladder (hypertonic bladder 15, ulcerative cystitis 5)	20	
					Renal Pain	8	
					Renal Cyst	5	
					Abnormality of the urine test and/or of the urine appearance (sterile pyuria)	5	
QUETIAPINE	45,711	44,529	2071	391	Non-urollogic medical conditions (acute kidney injury 609, renal failure 175, renal impairment 146, renal disorder 64, nephrogenic diabetes insipidus 38, polyuria 36, chronic kidney disease 35, oliguria 30, proteinuria 26, anuria 26, renal tubular necrosis 23, toxic nephropathy 22, renal injury 18, nephropathy 17, renal papillary necrosis 17, azotaemia 10, nephritis 10, tubulointerstitial nephritis 9, prerenal failure 8, end stage renal disease 7, focal segmental glomerulosclerosis 7, nephrotic syndrome 6)	1339	1998–2024
					LUTS (urinary incontinence 308, dysuria 140, pollakiuria 81, urinary hesitation 51, urgency 25, nocturia 17, micturition disorder 16)	638	
					Haematuria	33	
					Obstructive issues of the urinary tract (urinary retention 375, hydronephrosis 35, urinary tract obstruction 8, postrenal failure 6)	424	
					Conditions involving the bladder (bladder dilatation 19, hypertonic bladder 9)	28	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 16, leukocyturia 7, abnormal urine odour 6, haemoglobinuria 6, ketonuria 5)	40	
					Renal Pain	15	
					Ureterocoele	6	
					Kidney Enlargement	5	
					Non-urollogic medical conditions (acute kidney injury 462, renal failure 257, renal impairment 173, polyuria 117, renal disorder 115, chronic kidney disease 58, nephrogenic diabetes insipidus 19, anuria 17, end stage renal disease 16, tubulointerstitial nephritis 15, oliguria 14, diabetic nephropathy 14, nephrotic syndrome 9, renal injury 9, renal tubular disorder 8, renal hypertension 8, glycosuria 7, nephritis 6, nephropathy 5, hypertensive nephropathy 5, urate nephropathy 5)	1339	
ARIPRAZOLE	81,382	52,582	2837	1092	LUTS (urinary incontinence 574, dysuria 223, pollakiuria 195, urgency 55, nocturia 25,	1116	1998–2024

(continued on next page)

Table 3 (continued)

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
OLANZAPINE	74,981	64,011	4121	2122	micturition disorder 20, urinary hesitation 19, decreased frequency of micturition 5)		1996–2024
					Nephrolithiasis	48	
					Renal Pain	42	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 62, urine odour abnormal 30, proteinuria 26, urine abnormality 22, myoglobinuria 6, choluria 5, leukocyturia 5)	156	
					Haematuria	36	
					Conditions involving the bladder (bladder dilatation 31, bladder disorder 22, hypertonic bladder 20, interstitial cystitis 5, bladder rupture 5)	83	
					Urinary Tract Disorder	29	
					Obstructive issues of the urinary tract (urinary retention 402, hydronephrosis 23, renal colic 16, bladder obstruction 7, urinary tract obstruction 6)	454	
					Renal Cyst	10	
					Neurogenic Bladder	9	
					Genitourinary Symptom	9	
					Non-urologic medical conditions (acute kidney injury 784, renal failure 597, polyuria 314, renal impairment 214, glycosuria 123, renal disorder 121, chronic kidney disease 87, nephropathy 77, proteinuria 56, lupus nephritis 51, anuria 46, renal tubular necrosis 38, diabetic nephropathy 37, tubulointerstitial nephritis 29, oliguria 27, nephrogenic diabetes insipidus 24, renal injury 24, toxic nephropathy 18, nephrotic syndrome 12, nephrosclerosis 11, end-stage renal disease 10, nephritis 8, azotaemia 7, renal tubular disorder 6, prerenal failure 6)	2727	
					Obstructive issues of the urinary tract (urinary retention 474, hydronephrosis 23, urinary tract obstruction 10, bladder trabeculation 5)	512	
					LUTS (urinary incontinence 564, dysuria 206, pollakiuria 199, urinary hesitation 49, micturition urgency 43, nocturia 28, micturition disorder 21, urine flow decreased 11)	1121	
					Haematuria	135	
					Abnormality of the urine test and/or of the urine appearance (ketonuria 95, chromaturia 40, microalbuminuria 22, myoglobinuria 17, urine abnormality 14, urine odour abnormal 14, crystalluria 8, albuminuria 5)	215	
					Nephrolithiasis	49	
					Conditions involving the bladder (bladder dilatation 31, bladder disorder 29, atonic urinary bladder 9, bladder dysfunction 7, hypertonic bladder 6, interstitial cystitis 5, bladder discomfort 5)	92	
					Renal Cyst	27	
					Urinary Tract Disorder	24	
					Renal Pain	18	
					Neurogenic Bladder	16	
RISPERIDONE	107,418	71,515	3975	1392	Single Functional Kidney	16	1974–2024
					Urinoma	8	
					Renal Colic	6	
					LUTS (urinary incontinence 1079, pollakiuria 156, dysuria 155, nocturia 68, micturition urgency 38, micturition disorder 32, urinary hesitation 26, micturition frequency decreased 6)	1560	
					Non-urologic medical conditions (acute kidney injury 688, renal failure 391, renal impairment 279, polyuria 161, renal disorder 70, chronic kidney disease 66, anuria 64, oliguria 52, renal tubular necrosis 32, renal injury 21, azotaemia 20, end stage renal disease 16, nephrogenic diabetes insipidus 14, tubulointerstitial nephritis 13, nephropathy 12,	1955	

(continued on next page)

Table 3 (continued)

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
CITALOPRAM	29,751	28,336	1166	220	prerenal failure 12, diabetic nephropathy 10, nephrotic syndrome 8, renal tubular disorder 8 cases, nephropathy toxic 8, nephritis 5, glomerulonephritis 5)		1998–2024
					Obstructive issues of the urinary tract (urinary retention 505, hydronephrosis 41, urinary tract obstruction 7, calculus bladder 6 cases, postrenal failure 6 cases)	565	
					Haematuria	81	
					Conditions involving the bladder (bladder dilatation 58, bladder disorder 34, hypertonic bladder 21, hypotonic urinary bladder 7, cystitis interstitial 5, bladder pain 5)	130	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 49, glycosuria 12, proteinuria 30, myoglobinuria 25, urine abnormality 23, ketonuria 10, albuminuria 7, urine odour abnormal 6)	162	
					Nephrolithiasis	26	
					Urinary Tract Disorder	15	
					Neurogenic Bladder	15	
					Renal Pain	13	
					Renal Cyst	12	
					Kidney Enlargement	11	
					Non-urollogic medical conditions (acute kidney injury 264, renal failure 111, renal impairment 59, anuria 47 cases, chronic kidney disease 41, renal injury 19, renal tubular necrosis 18, nephropathy 17, nephropathy toxic 17, tubulointerstitial nephritis 16, renal disorder 12, oliguria 7, nephrocalcinosis 5, polyuria 5, nephrosclerosis 5)	643	
					Obstructive issues of the urinary tract (urinary retention 185, hydronephrosis 12, pyelocaliectasis 7, ureteric dilatation 6, bladder trabeculation 6)	216	
					LUTS (urinary incontinence 132, dysuria 72, pollakiuria 44, micturition disorder 34, micturition urgency 21, urinary hesitation 16, nocturia 6)	325	
					Conditions involving the bladder (hypertonic bladder 34, chromaturia 24, bladder pain 18, bladder disorder 16, bladder dilatation 14, bladder spasm 8, cystitis noninfective 7, atonic urinary bladder 7, loss of bladder sensation 7, bladder irritation 11)	146	
					Haematuria	26	
					Renal Pain	21	
					Nephrolithiasis	16	
					Renal Cyst	15	
					Abnormality of the urine test and/or of the urine appearance (crystalluria 12, proteinuria 8)	20	
					Urinary Tract Disorder	8	
					Renal Colic	7	
ESCITALOPRAM	16,703	15,320	878	101	Non-urollogic medical conditions (acute kidney injury 265, tubulointerstitial nephritis 58, renal impairment 46, renal failure 45, anuria 38, polyuria 18, renal tubular necrosis 12, glomerulonephritis 8, chronic kidney disease 8, renal disorder 7, focal segmental glomerulosclerosis 7, nephropathy toxic 5, tubulointerstitial nephritis and uveitis syndrome 6, oliguria 5)	528	2003–2024
					Haematuria	127	
					Obstructive issues of the urinary tract (urinary retention 91, hydronephrosis 10)	101	
					Urinary Tract Disorder	77	
					LUTS (urinary incontinence 87, pollakiuria 65, dysuria 26)	178	
					Abnormality of the urine test and/or of the urine appearance (proteinuria 11, ketonuria 6, chromaturia 6, urine abnormality 6)	29	

(continued on next page)

Table 3 (continued)

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
PAROXETINE	14,347	13,284	650	97	Conditions involving the bladder (bladder dilatation)	6	1993–2024
					Nephrolithiasis	12	
					Renal Pain	6	
					Vesicoureteral Reflux	6	
					Renal Colic	5	
					Non-urologic medical conditions (acute kidney injury 145, renal failure 78, renal impairment 47, oliguria 23, renal disorder 20, nephrogenic diabetes insipidus 15, renal ischaemia 12, renal tubular acidosis 11, tubulointerstitial nephritis 9, glomerulonephritis 7, renal tubular necrosis 7, anuria 6, renal salt-wasting syndrome 5, azotaemia 6, renal injury 5)	396	
					Obstructive issues of the urinary tract (urinary retention 109, pyelocaliectasis 11, hydronephrosis 5, urethral stenosis 5)	130	
					LUTS (incontinence 98, dysuria 30, pollakiuria 21, nocturia 17, urine flow decreased 8)	174	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 17, ketonuria 5)	22	
					Haematuria	11	
					Subcapsular Renal Haematoma	7	
					Conditions involving the bladder (bladder dilatation 7, bladder disorder 5, hypertonic bladder 6)	19	
					Nephrolithiasis	6	
					Renal Cyst	5	
FLUOXETINE	24,423	22,744	1007	184	Non-urologic medical conditions (acute kidney injury 310, nephropathy 7, renal impairment 39, oliguria 28, renal tubular necrosis 17, nephropathy toxic 15, polyuria 13, renal disorder 13, nephrosclerosis 12, anuria 12, chronic kidney disease 10, tubulointerstitial nephritis 8, renal failure 7)	559	1997–2024
					Obstructive issues of the urinary tract (urinary retention)	153	
					Haematuria	74	
					LUTS (dysuria 71, pollakiuria 68, micturition urgency 32, urinary tract discomfort 9, urinary incontinence 85, micturition disorder 6, nocturia 7, urinary hesitation 7)	285	
					Urinary Tract Disorder	52	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 28, proteinuria 6)	34	
					Renal Pain	15	
					Conditions involving the bladder (hypertonic bladder 11, bladder dilatation 10)	21	
					Nephrolithiasis	11	
					Non-urologic medical conditions (acute kidney injury 255, renal phospholipidosis 5, renal impairment 78, polyuria 36, renal disorder 31, oliguria 25, azotaemia 15, anuria 12, chronic kidney disease 12, glomerulonephritis minimal lesion 11, kidney fibrosis 9, nephrotic syndrome 9, renal vein thrombosis 9, nephropathy 8, nephrocalcinosis 8, renal tubular atrophy 7, renal failure 94)	624	
					Obstructive issues of the urinary tract (urinary retention 205, hydronephrosis 12, ureteric stenosis 11, pyelocaliectasis 6)	234	
					LUTS (urinary incontinence 219, dysuria 139, pollakiuria 102, urinary hesitation 52, micturition urgency 48, nocturia 37, micturition disorder 23, urinary tract discomfort 5, urine flow decreased 8)	633	
					Haematuria	94	
					Urinary Tract Disorder	52	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 34, proteinuria	82	
SERTRALINE	35,454	32,730	1453	484			1997–2024

(continued on next page)

Table 3 (continued)

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
DULOXETINE	13,850	11,546	748	151	22, urine abnormality 10, ketonuria 6, glycosuria 5, choluria 5)	89	2005–2024
					Conditions involving the bladder (bladder discomfort 24, bladder dilatation 17, bladder pain 15, hypertonic bladder 10, bladder dysfunction 6, bladder irritation 9, cystitis interstitial 18)		
					Renal Pain		
					Nephrolithiasis	11	
					Vesicoureteral Reflux	7	
					Non-urollogic medical conditions (acute kidney injury 138, renal impairment 64, renal failure 37, glomerulonephritis membranous 6, nephropathy toxic 14, renal disorder 13, polyuria 19, anuria 18)	7	
					Obstructive issues of the urinary tract (urinary retention)	309	
					Nephrolithiasis	137	
					LUTS (dysuria 68 cases, urinary incontinence 63, pollakiuria 34, urinary hesitation 12, urine flow decreased 9, micturition urgency 23, nocturia 21, micturition disorder 15)	86	
					Haematuria	245	
VENLAFAXINE	23,378	21,945	1297	270	Abnormality of the urine test and/or of the urine appearance (urine odour abnormal 15, chromaturia 12, urine abnormality 8, proteinuria 7)	39	1998–2024
					Urinary Tract Disorder	42	
					Non-urollogic medical conditions (acute kidney injury 397, renal failure 145, anuria 41, chronic kidney disease 30, renal impairment 27, oliguria 26, nephrotic syndrome 17, nephrogenic diabetes insipidus 14, renal tubular necrosis 12, azotaemia 10, renal papillary necrosis 9, renal injury 8, tubulointerstitial nephritis 7, polyuria 6, kidney fibrosis 6, renal artery stenosis 6)	5	
					LUTS (urinary incontinence 184, dysuria 87, pollakiuria 46, micturition urgency 34, micturition disorder 17, urinary hesitation 13, urinary straining 6, nocturia 5)	761	
					Obstructive issues of the urinary tract (urinary retention 117, hydronephrosis 16, ureteric stenosis 1, ureteric obstruction 6, bladder trabeculation 6)	392	
					Haematuria	156	
					Urinary Tract Disorder	68	
					Nephrolithiasis	49	
					Conditions involving the bladder (hypertonic bladder 27, bladder dilatation 13, bladder irritation 7)	28	
					Abnormality of the urine test and/or of the urine appearance (proteinuria 23, chromaturia 12, leukocyturia 9, albuminuria 8, microalbuminuria 5 cases, crystalluria 5, hypernatruria 5)	47	
AMITRIPTYLINE	17,982	16,209	1013	118	Renal Pain	67	1969–2024
					Kidney Enlargement	15	
					Non-urollogic medical conditions (acute kidney injury 189, renal failure 68, renal impairment 44, nephropathy toxic 25, tubulointerstitial nephritis 19, polyuria 19, renal disorder 17, azotaemia 13, nephrosclerosis 10, anuria 10, chronic kidney disease 6, kidney fibrosis 5)	9	
					Obstructive issues of the urinary tract (urinary retention 170, hydronephrosis 9, pyelocaliectasis 9)	425	
					Nephrolithiasis	188	
					LUTS (dysuria 74, urinary incontinence 93, pollakiuria 34, micturition urgency 15, nocturia 11, urinary hesitation 8)	133	
						235	

(continued on next page)

Table 3 (continued)

Drug Name	Total ADR Cases	Serious cases (including deaths)	Renal and Urinary Disorders	Renal and Urinary Disorders (numbers following unmasking analysis)	Breakdown of selected Reactions	Number of cases of selected reactions	Timeline of ADR Reporting
CLOMIPRAMINE	2470	2360	157	139	Conditions involving the bladder (bladder disorder 37, cystitis interstitial 5, cystitis noninfective 5)	47	1986–2024
					Renal Mass	31	
					Renal Pain	29	
					Abnormality of the urine test and/or of the urine appearance (chromaturia 21, urine abnormality 8)	29	
					Haematuria	18	
					Urinary Tract Disorder	6	
					Renal Cyst	5	
					Non-urologic medical conditions (acute kidney injury 63, nephrogenic diabetes insipidus 5, renal impairment 11, renal hypertension 8, polyuria 40)	127	
					Obstructive issues of the urinary tract (urinary retention)	16	
					LUTS (dysuria 13, micturition frequency decreased 5, urinary incontinence 11, urinary hesitation 10)	39	
					Abnormality of the urine test and/or of the urine appearance (chromaturia)	7	

688 cases), quetiapine ($N = 609$ cases), and aripiprazole ($N = 462$ cases). The second most common ADR was urinary incontinence with risperidone ($N = 1079$ cases), olanzapine ($N = 564$), and aripiprazole ($N = 402$ cases). High rates of urinary retention ($N = 375$ cases) were recorded with quetiapine. With regards to ADs, high occurrences of acute kidney injury were identified with the following medications: venlafaxine ($N = 397$ cases); fluoxetine ($N = 310$ cases); escitalopram ($N = 265$ cases); citalopram ($N = 264$ cases); sertraline ($N = 255$ cases); amitriptyline ($N = 189$ cases); paroxetine ($N = 145$ cases); duloxetine ($N = 138$ cases); and clomipramine ($N = 63$ cases). Urinary retention was common with citalopram ($N = 185$ cases); amitriptyline ($N = 170$ cases); fluoxetine ($N = 153$ cases); paroxetine ($N = 109$ cases); clomipramine ($N = 16$ cases). Urinary incontinence was mostly recorded with sertraline ($N = 219$ cases) and venlafaxine ($N = 184$ cases).

With regards to esketamine, notable conditions included LUTS ($N = 73$ cases), specifically, pollakiuria ($N = 29$ cases); micturition urgency ($N = 18$ cases); urinary incontinence ($N = 21$ cases). Ketamine was associated to nephrolithiasis ($N = 90$ cases); acute kidney injury ($N = 84$ cases); urinary tract disorder ($N = 50$ cases); hematuria ($N = 26$ cases); and hydronephrosis ($N = 26$ cases).

The disproportionality analysis described the ROR for renal and urinary disorders associated with esketamine and ketamine, compared to each other and to various classes of molecules, including SGAs, SSRIs, SNRIs, and TCAs. Detailed results are reported in Table 4. Ketamine showed significantly higher odds of renal and urinary disorders compared to SGAs, SSRIs, SNRIs, and TCAs (respectively, $ROR = 1.38$; 95 % CI = 0.52, 0.13; $ROR = 2.5$; 95 % CI = 1.12, 0.71; $ROR = 1.98$; 95 % CI = 0.9, 0.47; and $ROR = 3.31$; 95 % CI = 1.45, 0.94). Conversely, esketamine generally showed lower or comparable odds of renal and urinary disorders compared to ketamine, though not always significantly so. Indeed, esketamine had 0.82 times higher odds of renal and urinary disorders compared to ketamine, but the CI indicated that this result was not statistically significant neither for general cases ($ROR = 0.82$; 95 % CI = 0.06, −0.45), nor for selected ‘serious’ cases ($ROR = 0.79$; 95 % CI = 0.02, −0.49). Similarly, no significant results were here identified with esketamine vs. SGAs (general cases: $ROR = 1.13$; 95 % CI = 0.30, −0.04; serious cases: $ROR = 1.85$; 95 % CI = 0.005, −0.33), esketamine vs. SSRIs (general cases: $ROR = 2.05$; 95 % CI = 0.9, 0.5; serious cases: $ROR = 1.9$; 95 % CI = 0.82, 0.45), esketamine vs. SNRIs (general cases: $ROR = 1.63$; 95 % CI = 0.7, 0.3; serious cases: $ROR = 1.46$; 95 % CI = 0.57, 0.19), and esketamine vs. TCAs (general cases:

Table 4
Disproportionality measures related to urological adverse events of ketamine and esketamine versus antidepressant and antipsychotic drugs.

	Odds of renal and urinary disorder	Odds of renal and urinary disorder (‘serious’ cases)
Esketamine versus Ketamine	$ROR = 0.82$; 95 % CI = 0.06, −0.45	$ROR = 0.79$; 95 % CI = 0.02, −0.49
Esketamine compared to SGAs	$ROR = 1.13$; 95 % CI = 0.30, −0.04	$ROR = 0.85$; 95 % CI = 0.005, −0.33
Esketamine compared to SSRIs	$ROR = 2.05$; 95 % CI = 0.9, 0.5	$ROR = 1.9$; 95 % CI = 0.82, 0.45
Esketamine compared to SNRIs	$ROR = 1.63$; 95 % CI = 0.7, 0.3	$ROR = 1.46$; 95 % CI = 0.57, 0.19
Esketamine compared to TCAs	$ROR = 2.7$; 95 % CI = 1.2, 0.8	$ROR = 2.47$; 95 % CI = 1.14, 0.67
Ketamine versus Esketamine	$ROR = 1.22$; 95 % CI = 0.45, −0.06	–
Ketamine compared to SGAs	$ROR = 1.38$; 95 % CI = 0.52, 0.13	–
Ketamine compared to SSRIs	$ROR = 2.5$; 95 % CI = 1.12, 0.71	–
Ketamine compared to SNRIs	$ROR = 1.98$; 95 % CI = 0.9, 0.47	–
Ketamine compared to TCAs	$ROR = 3.31$; 95 % CI = 1.45, 0.94	–

Abbreviations: CI: confidence intervals; ROR: Relative odds ratio; SGAs: second generation antipsychotics; SNRIs: serotonin noradrenaline reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.
General Interpretation:
 $ROR < 1$: Lower odds of renal and urinary disorders compared to the reference group.
 $ROR > 1$: Higher odds of renal and urinary disorders compared to the reference group.
The 95 % CI provide a range of values within which the true ROR is expected to lie with 95 % confidence.
95 % CI containing zero: The result is not statistically significant.
95 % CI not containing zero: The result is statistically significant.

$ROR = 2.7$; 95 % CI = 1.2, 0.8; serious cases: $ROR = 2.47$; 95 % CI = 1.14, 0.67). Finally, ketamine compared with esketamine was associated with 1.22 times higher odds of renal and urinary disorders, but this result was not significant (general cases: $ROR = 1.22$; 95 % CI = 0.45, −0.06).

The findings of this study must be interpreted within the context of

the limitations inherent to FAERS data. The lack of stratification by specific drug formulations, dosing regimens, or routes of administration may complicate direct comparisons.

4. Discussion

The study analyzed both ketamine and esketamine urological safety in comparison with SGAs and a range of antidepressant drugs, including SSRIs, SNRIs, and TCAs. The safety profile of esketamine must be interpreted within the context of its FDA-approved indications, as the associated treatment protocols differ significantly between TRD and MDSI. For TRD, the combination of esketamine with SSRIs or SNRIs may influence adverse event reporting differently than in MDSI, where esketamine is used alongside a broader range of SoC treatments, including antipsychotics such as quetiapine, olanzapine, and aripiprazole. These antipsychotics are known to have distinct safety profiles, including potential urological adverse effects, which could confound the analysis of esketamine's direct impact.

Current data may indicate that ketamine is associated with a higher risk of renal and urinary disorders compared to SSRIs, TCAs, and SGAs. Esketamine showed a slightly lower risk than ketamine, potentially due to its different pharmacological profile and administration routes. This is consistent with (Findeis et al., 2020b), who preliminarily suggested the relative urothelial safety of esketamine with regard to urological symptoms such as urinary tract infections, cystitis, and other urinary disorders. Conversely, the urological lack of safety of both recreational and prescribed ketamine itself has been extensively reported [19; 26–29]. Although the exact mechanism by which ketamine causes uropathy is not fully understood, several theories have been hypothesized, including a *direct toxicity to the urothelium*, where ketamine and its metabolites may directly irritate the bladder lining, leading to

inflammation and fibrosis; a *neurogenic effect*, possibly affecting the central and peripheral nervous systems, potentially altering bladder function; and an *immune-mediated response*, related to the chronic ketamine use triggering immune responses that contribute to persistent bladder inflammation, enhanced cell apoptosis and damage (Anderson et al., 2022; Jhang et al., 2023). Nonetheless, (Ng et al., 2021) suggest that there is no evidence that ketamine and/or esketamine treatment in adults with mood disorders is associated with urological dysfunction.

However, major concerns remain regarding an effective protocol to maintain the clinical antidepressant effect of ketamine seen with the acute administration and the safety, including urological, of ketamine and esketamine in the long term (Brucculeri et al., 2023; Molero et al., 2018). This distinction is critical, particularly considering the documented urological toxicity which has been described in chronic abusers, which includes symptoms such as dysuria, urgency, and hematuria (Schifano et al., 2021). Thus, data from this study are particularly noteworthy given the longstanding concerns about the urological toxicity of both ketamine and esketamine. The findings of this study contribute valuable insights to this ongoing discussion, suggesting that esketamine may offer a relatively safe urological profile, although there needs to be a balanced evaluation of therapeutic benefits against potential risks. As indicated by recent studies, intravenous (IV) ketamine demonstrates rapid and robust antidepressant effects in adults with TRD, but also carries a higher risk of adverse events, including urological toxicity (Ng et al., 2021).

Overall, an assessment of urological complications related to ketamine/esketamine use in both elective and emergency urology settings is suggested by the British Association of Urological Surgeons Consensus (Belal et al., 2024). In line with this, it is here proposed a urological/medical assessment which may need to be carried out to be done before considering any ketamine/esketamine prescribing (Fig. 1).

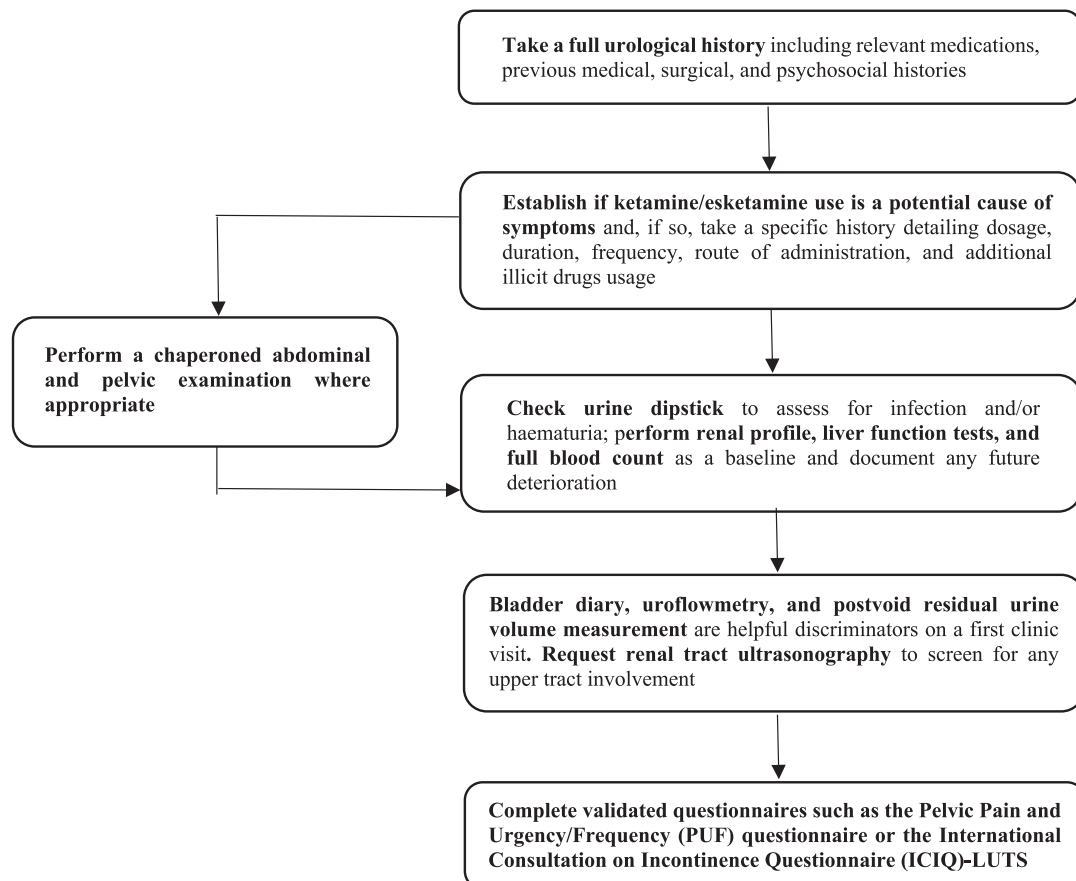


Fig. 1. Assessment and further investigation steps for urological symptoms, particularly related to potential ketamine/esketamine use.

Overall, several psychotropic drugs are commonly implicated in urinary symptoms, especially LUTS (Dobrek, 2023; Trinchieri et al., 2021; Winkler et al., 2021). They include opioids, anticholinergics, TCA, SNRI, SSRI, and antipsychotics. Some of them (e.g., anticholinergics, antipsychotics with strong anticholinergic properties, such as clozapine, olanzapine, quetiapine) act as muscarinic receptor blockers at the bladder level, reducing detrusor muscle contractility, inhibiting bladder contractions, and leading to retention. Others (e.g., opioids) can alter neural control of bladder function. Although the lithium-related renal toxicity has been extensively described (Bosi et al., 2023), fewer studies have examined the urological safety of antipsychotics and antidepressants in general (Damba et al., 2022). However, a recent meta-analysis (Ong et al., 2024) aiming at quantifying the risk of renal impairment associated with atypical antipsychotics showed that out of a total of 514,710 patients (221,873 on atypical antipsychotics with chronic kidney disease versus 292,837 controls), patients taking atypical antipsychotics showed an elevated risk of renal impairment, with a pooled risk ratio of 1.34 (95 % CI 1.23–1.47). A subgroup analysis revealed that the use of atypical antipsychotics was linked to a heightened risk of both acute kidney injury (RR 1.51, 95 % CI 1.34–1.71) and chronic kidney disease (RR 1.23, 95 % CI 1.12–1.35). Urinary incontinence was widely associated to urinary incontinence (Trinchieri et al., 2021; Arasteh et al., 2021), something wrong in this statement in relation to olanzapine and quetiapine's anticholinergic effects contributing to both urinary retention and incontinence, and their sedating effect, which may reduce the awareness of the need to urinate; risperidone alpha-adrenergic blocking properties that can lead to relaxation of the urethral sphincter, resulting in incontinence. Aripiprazole's mechanism related to urinary incontinence is less clear but may involve its partial agonist activity at dopamine receptors and its effect on serotonin receptors, potentially disrupting the balance of neurotransmitters that control bladder function. With regards to antidepressants, those mechanisms of urinary incontinence/retention associated are related to anticholinergic properties, inhibiting parasympathetic activity, reducing bladder muscle contractions and leading to urinary retention. They also have alpha-adrenergic blocking effects that can relax the urethral sphincter, potentially causing incontinence. This is common with TCAs, e.g., amitriptyline (Faure Walker et al., 2016). The serotonergic modulation typical of SSRIs and SNRIs can enhance detrusor muscle activity, causing urgency and incontinence. Altered serotonin levels can also affect the neural circuits involved in bladder control. Similarly, elevated norepinephrine levels due to SNRIs can lead to detrusor overactivity, contributing to urinary incontinence.

Urinary side effects significantly impact the quality of life of patients, contributing to discomfort, embarrassment, and social withdrawal. Our findings align with the need for more nuanced safety protocols, as cardiovascular safety risks (e.g., blood pressure elevations) are often underestimated in intravenous, nasal, and inhaled formulations of ketamine and esketamine. This oversight is particularly critical in early-phase drug development pipelines. Moreover, urinary side effects can lead to poor adherence to psychotropic medications, exacerbating underlying mental health conditions. Thus, recognizing these side effects early and managing them effectively is crucial; for urinary side effects, management strategies should include: i) medication Adjustment, reducing doses or switching to psychotropics with a lower risk of urinary side effects; ii) symptom management, using anticholinergic agents to manage incontinence or alpha-blockers for retention, under careful supervision; iii) non-pharmacological approaches, such as behavioural interventions such as bladder training and pelvic floor exercises (Winkler et al., 2021). In clinical practice, esketamine is frequently co-administered with other psychotropic agents such as SGAs and lithium, particularly in the management of TRD. This highlights the need for tailored treatment approaches that consider potential synergistic benefits and overlapping safety concerns, including metabolic, cardiovascular, and urological risks. Psychotropic safety protocols must integrate insights from multiple specialties to ensure comprehensive

adverse event management. This study provides a case example of how specific safety concerns can vary significantly across formulations and drug classes, necessitating tailored oversight strategies. Clinicians should be educated on the urinary side effects of psychotropic drugs in order to identify specific risk factors and enhance patient care and treatment outcomes.

5. Limitations of the study

Although pharmacovigilance studies are crucial for monitoring the safety of drugs post-marketing, they do have several limitations: one limitation of this study relates to the 'submerged' data component associated with ketamine. Unlike esketamine, which is used in controlled medical settings, ketamine is frequently misused recreationally at doses significantly higher than therapeutic recommendations. These instances often occur outside healthcare supervision, leading to underreporting of adverse events in pharmacovigilance databases. Indeed, many ADRs might have not been reported by healthcare professionals or patients, leading to incomplete data. It is important to note that the FDA Adverse Event Reporting System (FAERS) data used in this study does not stratify adverse event reports by specific drug formulations, dosing regimens, or routes of administration. As such, the esketamine data predominantly reflect nasal spray formulations approved for TRD or MDD, while ketamine data encompass diverse off-label and in-label uses with significant variability in dosing and frequency. This limitation highlights the need for more granular safety surveillance systems to improve the clinical interpretation of adverse event profiles. Reporting bias can occur due to factors like the notoriety of a drug, media coverage, litigation fears, and variations in regulatory requirements and reporting practices across countries, leading to misinterpretation. Moreover, spontaneously reporting systems, such as the FAERS, are passive and rely on voluntary reporting, which might not capture all ADRs and may have a delay in detecting safety signals; the data reported can be incomplete, inaccurate, or inconsistent: missing information about dosage, patient history, and concomitant medications can hinder proper assessment. The causality assessment is always challenging due to confounding factors such as underlying diseases, concurrent medications, and population differences. Finally, unlike RCTs, pharmacovigilance studies often lack control groups, making it difficult to attribute ADRs solely to the drug without considering other variables. Future studies should leverage stratified datasets and real-world registries to provide more nuanced insights into the safety profiles of these drugs.

6. Conclusions

The findings presented in this study are of interest, especially in light of the previous concerns regarding the urological toxicity of both ketamine and esketamine. Current data may support the relatively favorable tolerability profile of ketamine and especially esketamine which are being used for the treatment of patients with severe and TRD. However, present findings strongly suggest the need of more extensive studies weighing the risks and monitoring for adverse effects in order to explore long-term safety and optimize treatment protocols. Indeed, the potential risks associated with any treatments warrant ongoing vigilance and rigorous assessment. Given the limited data on esketamine urological toxicity beyond the current study, these findings could significantly advance the understanding and clinical management of esketamine and ketamine in treating mood disorders.

The aggregated nature of FAERS data has important implications for the stakeholders who rely on such datasets for decision-making. For regulatory bodies, academic researchers and the pharmaceutical industry, the absence of stratification in adverse event reporting complicates the evaluation of safety profiles for drugs like esketamine and ketamine, where formulations, dosing regimens, and use cases vary widely. Therefore, there is an urgent need for datasets with real-world

evidence from more specific and granular sources, such as clinical registries and post-marketing studies. The findings of this study emphasize the need for a concerted effort to incorporate stratified and contextualized reporting mechanisms to enhance the reliability of safety data, improve risk management strategies, and ultimately contribute to better patient care.

Ethics statement

The study complies with the principles of the Declaration of Helsinki, and all applicable guidelines for ethical research practices were strictly followed. This study did not require formal ethics approval, as it did not involve direct interaction with human subjects or the collection of new personal data.

Funding

This research received no external funding. Institutional Review Board Statement: Not applicable. Informed Consent Statement: Not applicable.

CRediT authorship contribution statement

S. Chiappini: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **A. Guirguis:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **N. Schifano:** Writing – review & editing, Writing – original draft. **J. M. Corkery:** Writing – review & editing. **F. Semeraro:** Writing – review & editing. **A. Mosca:** Writing – review & editing. **G. D’Andrea:** Writing – review & editing. **G. Duccio Papanti:** Writing – review & editing. **D. Arillotta:** Writing – review & editing. **G. Floresta:** Writing – review & editing. **G. Martinotti:** Writing – review & editing. **F. Schifano:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

F.S. was a member of both the UK Advisory Council on the Misuse of Drugs (ACMD; 2011–2019) and of the EMA Advisory Board (2011–2023; Psychiatry). J.M.C. is a member of the ACMD’s Novel Psychoactive Substances and Technical Committees. G.M. has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Recordati. A.G., S.C., R.V.-S., D.H.: declare no conflict of interest.

Data availability

Data will be made available on request.

References

- Anderson, D.J., Zhou, J., Cao, D., McDonald, M., Guenther, M., Hasoon, J., Viswanath, O., Kaye, A.D., Urts, I., 2022. Ketamine-induced cystitis: a comprehensive review of the urologic effects of this psychoactive drug. *Health Psychol. Res.* 10 (3), 38247. <https://doi.org/10.52965/001c.38247>. PMID: 36118982; PMCID: PMC9476224.
- Arasteh, A., Mostafavi, S., Zununi Vahed, S., Mostafavi Montazeri, S.S., 2021. An association between incontinence and antipsychotic drugs: a systematic review. *Biomed. Pharmacother.* 142, 112027. <https://doi.org/10.1016/j.biopha.2021.112027>.
- Bahr, R., Lopez, A., Rey, J.A., 2019. Intranasal Esketamine (Spravato™) for use in treatment-resistant depression in conjunction with an Oral antidepressant. *P T* 44 (6), 340–375.
- Baker, S.C., Shabir, S., Georgopoulos, N.T., Southgate, J., 2016. Ketamine-induced apoptosis in Normal human urothelial cells. *Am. J. Pathol.* 186 (5). <https://doi.org/10.1016/j.ajpath.2015.12.014>.
- Belal, M., Downey, A., Doherty, R., Ali, A., Hashim, H., Kozan, A., Kujawa, M., Pakzad, M., Rashid, T., Osman, N., Sahai, A., Biers, S., on behalf of the BAUS Section

- of Female, 2024. Neurological and urodynamic urology. British association of urological surgeons consensus statements on the management of ketamine uropathy. *BJU Int.* <https://doi.org/10.1111/bju.16404>.
- Bihan, K., Lebrun-Vignes, B., Funck-Brentano, C., Salem, J.E., 2020. Uses of pharmacovigilance databases: an overview. *Therapie* 75 (6), 591–598. <https://doi.org/10.1016/j.jtherap.2020.02.022>. Epub 2020 Feb 26. PMID: 32169289.
- Bosi, A., Clase, C.M., Ceriani, L., Sjölander, A., Fu, E.L., Runesson, B., Chang, Z., Landén, M., Bellocchio, R., Elinder, C.G., Carrero, J.J., 2023. Absolute and relative risks of kidney outcomes associated with Lithium vs valproate use in Sweden. *JAMA Netw. Open* 6 (7), e2322056. <https://doi.org/10.1001/jamanetworkopen.2023.22056>. PMID: 37418264; PMCID: PMC10329212.
- Boudieu, L., Mennetrier, M., Llorca, P.-M., Samalin, L., 2023. The efficacy and safety of intranasal formulations of ketamine and Esketamine for the treatment of major depressive disorder: a systematic review. *Pharmaceutics* 15 (12), 2773. <https://doi.org/10.3390/pharmaceutics15122773>.
- Bruculeri, M., Johnson, D., Yang, Y., Renne, H., 2023. Ketamine-induced acute interstitial nephritis. *Kidney Int. Rep.* 8 (4). <https://doi.org/10.1016/j.ekir.2022.12.015>.
- Castro, M., Wilkinson, S.T., Al Jurdi, R.K., Petrillo, M.P., Zaki, N., Borentain, S., Fu, D.J., Turkoz, I., Sun, L., Brown, B., Cabrera, P., 2023. Efficacy and safety of Esketamine nasal spray in patients with treatment-resistant depression who completed a second induction period: analysis of the ongoing SUSTAIN-3 study. *CNS Drugs* 37 (8), 715–723. <https://doi.org/10.1007/s40263-023-01026-3> (Epub 2023 Aug 9. PMID: 37558912; PMCID: PMC10439056).
- Chiappini, S., d’Andrea, G., De Filippis, S., Di Nicola, M., Andriola, I., Bassetti, R., Barlati, S., Pettorruso, M., Sensi, S., Clerici, M., Dell’Osso, B., Vita, A., Martinotti, G., 2023. Esketamine in treatment-resistant depression patients comorbid with substance-use disorder: a viewpoint on its safety and effectiveness in a subsample of patients from the REAL-ESK study. *Eur. Neuropsychopharmacol.* 74, 15–21. <https://doi.org/10.1016/j.euroneuro.2023.04.011>.
- Chu, P.S., Ma, W.K., Wong, S.C., Chu, R.W., Cheng, C.H., Wong, S., Tse, J.M., Lau, F.L., Yiu, M.K., Man, C.W., 2008. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int.* 102 (11), 1616–1622. <https://doi.org/10.1111/j.1464-410X.2008.07920.x>. Epub 2008 Aug 1. PMID: 18680495.
- Daly, E.J., Trivedi, M.H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A.R., Hough, D., Thase, M.E., Zajecka, J., Winokur, A., Divacka, I., Fagioli, A., Cubala, W.J., Bitter, I., Blier, P., Shelton, R.C., Molero, P., Manji, H., Drevets, W.C., Singh, J.B., 2019. Efficacy of Esketamine nasal spray plus Oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 76 (9), 893–903. <https://doi.org/10.1001/jamapsychiatry.2019.1189>.
- Damba, J.J., Bodenstein, K., Lavin, P., et al., 2022. Psychotropic drugs and adverse kidney effects: a systematic review of the past decade of research. *CNS Drugs* 36 (10), 1049–1077. <https://doi.org/10.1007/s40263-022-00952-y>.
- D’Andrea, G., di Marco, O., Semeraro, F.M., Carullo, R., Sensi, S.L., Pettorruso, M., Martinotti, G., 2023a. Intranasal esketamine as tool for rapid cycling bipolar disorder: a case report of successful mood stabilization. *Psychiatry Res. Case Rep.* 2 (2). <https://doi.org/10.1016/j.psycr.2023.100188>.
- D’Andrea, G., Pettorruso, M., Di Lorenzo, G., Mancusi, G., McIntyre, R.S., Martinotti, G., 2023b. Rethinking ketamine and esketamine action: are they antidepressants with mood-stabilizing properties? *Eur. Neuropsychopharmacol.* 70. <https://doi.org/10.1016/j.euroneuro.2023.02.010>.
- Dobrek, L., 2023. Lower urinary tract disorders as adverse drug reactions—a literature review. *Pharmaceutics* 16 (7), 1031. <https://doi.org/10.3390/ph16071031>.
- Faure Walker, N., Brinchmann, K., Batura, D., 2016. Linking the evidence between urinary retention and antipsychotic or antidepressant drugs: a systematic review. *Neurol. Urology* 35 (8), 866–874. <https://doi.org/10.1002/nau.22851>.
- FDA, 2019. FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified>. Accessed 07 August, 2024.
- Fedgchin, M., Trivedi, M., Daly, E.J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Amele, H.V.D., Preskorn, S., Manji, H., Hough, D., Drevets, W.C., Singh, J.B., 2019. Efficacy and safety of fixed-dose Esketamine nasal spray combined with a new Oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *Int. J. Neuropsychopharmacol.* 22 (10), 616–630. <https://doi.org/10.1093/ijnp/pyz039>.
- Findeis, H., Sauer, C., Cleare, A., Bauer, M., Ritter, P., 2020a. Urothelial toxicity of esketamine in the treatment of depression. *Psychopharmacology (Berl)* 237 (11). <https://doi.org/10.1007/s00213-020-05611-y>.
- Findeis, H., Sauer, C., Cleare, A., Bauer, M., Ritter, P., 2020b. Urothelial toxicity of esketamine in the treatment of depression. *Psychopharmacology (Berl)* 237 (11), 3295–3302. <https://doi.org/10.1007/s00213-020-05611-y>. Epub 2020 Jul 26. PMID: 32712681; PMCID: PMC7561544.
- Frias, B., Santos, J., Morgado, M., Sousa, M.M., Gray, S.M., McCloskey, K.D., Allen, S., Cruz, F., Cruz, C.D., 2015. The role of brain-derived neurotrophic factor (BDNF) in the development of neurogenic detrusor overactivity (NDO). *J. Neurosci.* 35 (5), 2146–2160.
- Jhang, J.F., Bider, L.A., Kuo, H.C., 2023. Pathophysiology, clinical presentation, and management of ketamine-induced cystitis. *Tzu Chi. Med. J.* 35 (3), 205–212. <https://doi.org/10.4103/tcmj.tcmj.94.23>. PMID: 37545795; PMCID: PMC10399845.
- Martinotti, G., Vita, A., Fagioli, A., Maina, G., Bertolino, A., Dell’Osso, B., Siracusano, A., Clerici, M., Bellomo, A., Sani, G., d’Andrea, G., Chiaie, R.D., Conca, A., Barlati, S., Di Lorenzo, G., De Fazio, P., De Filippis, S., Nicolò, G., Rosso, G., Valchera, A., Nucifora, D., Di Mauro, S., Bassetti, R., Martiadis, V.,

- Olivola, M., Belletti, S., Andriola, I., Di Nicola, M., Pettorruso, M., McIntyre, R.S., di Giannantonio, M., REAL-ESK Study Group, 2022. Real-world experience of esketamine use to manage treatment-resistant depression: A multicentric study on safety and effectiveness (REAL-ESK study). *J. Affect. Disord.* 319, 646–654. <https://doi.org/10.1016/j.jad.2022.09.043>.
- Molero, P., Ramos-Quiroga, J.A., Martín-Santos, R., Calvo-Sánchez, E., Gutiérrez-Rojas, L., Meana, J.J., 2018. Antidepressant efficacy and tolerability of ketamine and Esketamine: a critical review. *CNS Drugs* 32 (5), 411–420. <https://doi.org/10.1007/s40263-018-0519-3>.
- Ng, J., Lui, L.M.W., Rosenblatt, J.D., et al., 2021. Ketamine-induced urological toxicity: potential mechanisms and translation for adults with mood disorders receiving ketamine treatment. *Psychopharmacology (Berl)* 238 (4), 917–926. <https://doi.org/10.1007/s00213-021-05767-1>.
- Ochs-Ross, R., Daly, E.J., Zhang, Y., Lane, R., Lim, P., Morrison, R.L., Hough, D., Manji, H., Drevets, W.C., Sanacora, G., Steffens, D.C., Adler, C., McShane, R., Gaillard, R., Wilkinson, S.T., Singh, J.B., 2020. Efficacy and safety of Esketamine nasal spray plus an Oral antidepressant in elderly patients with treatment-resistant depression—TRANSFORM-3. *Am. J. Geriatr. Psychiatr.* 28 (2), 121–141. <https://doi.org/10.1016/j.jagp.2019.10.008>.
- Ong, L.T., Chee, N.M.Z., Loh, A.J.C., 2024. Risk of renal impairment in atypical antipsychotics: a systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* <https://doi.org/10.1007/s00228-024-03714-5>.
- Popova, V., Daly, E.J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M.E., Shelton, R.C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., Singh, J.B., 2019. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am. J. Psychiatry* 176 (6), 428–438. <https://doi.org/10.1176/appi.ajp.2019.19020172>. Epub 2019 may 21. Erratum in: *am J psychiatry*. 2019 Aug 1;176(8):669. doi: 10.1176/appi.ajp.2019.1768correction1. PMID: 31109201.
- Prasad, K., Jaeschke, R., Wyer, P., Keitz, S., Guyatt, G., 2008. Evidence-based medicine teaching tips working group. Tips for teachers of evidence-based medicine: understanding odds ratios and their relationship to risk ratios. *J. Gen. Intern. Med.* 23 (5), 635–640. <https://doi.org/10.1007/s11606-007-0453-4>.
- Salahudeen, M.S., Wright, C.M., Peterson, G.M., 2020. Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. *Ther. Adv. Drug Saf.* 11, 2042098620937899. Published 2020 Jul 23. <https://doi.org/10.1177/2042098620937899>.
- Schifano, N., Chiappini, S., Castiglione, F., Salonia, A., Schifano, F., 2021. Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European medicines agency (EMA) and the UK yellow card scheme pharmacovigilance database-related reports. *Low Urin Tract Symptoms*. 13 (2), 230–237. <https://doi.org/10.1111/luts.12355>. Epub 2020 Oct 9. PMID: 33037767.
- Szumilas, M., 2010. Explaining odds ratios [published correction appears in *J Can Acad Child Adolesc Psychiatry*. 2015 Winter;24(1):58]. *J. Can. Acad. Child Adolesc. Psychiatry* 19 (3), 227–229.
- Trinchieri, M., Perletti, G., Magri, V., Stamatiou, K., Montanari, E., Trinchieri, A., 2021. Urinary side effects of psychotropic drugs: a systematic review and metanalysis. *Neurourol. Urodyn.* 40 (6), 1333–1348. <https://doi.org/10.1002/nau.24695>. Epub 2021 May 18. PMID: 34004020.
- Wajs, E., Aluisio, L., Holder, R., Daly, E.J., Lane, R., Lim, P., George, J.E., Morrison, R.L., Sanacora, G., Young, A.H., Kasper, S., Sulaiman, A.H., Li, C.T., Paik, J.W., Manji, H., Hough, D., Grunfeld, J., Jeon, H.J., Wilkinson, S.T., Drevets, W.C., Singh, J.B., 2020. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a Phase 3, open-label study (SUSTAIN-2). *J. Clin. Psychiatry* 81 (3), 19m12891. <https://doi.org/10.4088/JCP.19m12891>.
- Winkler, D., Grohmann, R., Friedrich, M.E., Toto, S., Bleich, S., Seifert, J., Konstantinidis, A., Shariat, S.F., Kasper, S., Pjrek, E., 2021. Urological adverse drug reactions of psychotropic medication in psychiatric inpatients - a drug surveillance report from German-speaking countries. *J. Psychiatr. Res.* 144, 412–420. <https://doi.org/10.1016/j.jpsychires.2021.10.026>. Epub 2021 Oct 27. PMID: 34741839.
- Yeh, C.H., Chen, B.H., Tseng, X.W., et al., 2021. Intravesical instillation of norketamine, a ketamine metabolite, and induced bladder functional changes in rats. *Toxics* 9 (7), 154. . Published 2021 Jun 30. <https://doi.org/10.3390/toxics9070154>.