Drugs associated the most with Retroperitoneal Fibrosis: assessment of the 1969-2025 Food and Drug Administration (FDA) pharmacovigilance database

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Abstract

Introduction and Objectives

Retroperitoneal fibrosis (RPF) is a rare fibroinflammatory disorder characterized by the development of fibrotic tissue around the abdominal aorta, often leading to ureteral entrapment and renal dysfunction. Several pharmacological agents have been implicated as potential triggers. Despite scattered case reports and limited series, comprehensive quantitative assessments of drug-related RPF signals remain scarce. This study aimed to identify and quantify signals of disproportionate reporting of RPF associated with specific medications using data from a large pharmacovigilance database.

Methods

The FDA Adverse Event Reporting System (FAERS) was queried from 1969 to 2025 to identify RPF-related adverse event reports. Drugs associated with more than twenty RPF reports were included in a disproportionality analysis; this threshold was arbitrarily defined to focus on medications with a relatively higher volume of reports. This selection aimed to ensure adequate statistical power and reduce noise from underreported associations. For each, the Reporting Odds Ratio (ROR), 95% Confidence Intervals (CI), Proportional Reporting Ratio (PRR), chi-square values, and p-values were calculated. A signal was considered statistically significant when PRR > 2, chi-square > 4, and $p < 0.05$. The total number of reports in the FAERS database was 30,668,520.

Results

A total of 1,013 RPF cases were identified. Of these, 392 (38.7%) were linked to twelve drugs, each associated with more than twenty RPF reports. Methysergide showed the strongest association (ROR: 5332.28; 95% CI: 4292.96–6623.21; PRR: 4604.65; chi-square: 429546.30; $p < 0.0001$), followed by pergolide (ROR: 923.85; 95% CI: 686.60–1243.09; PRR: 897.76; chi-square: 40148.64; $p < 0.0001$) and bromocriptine (ROR: 311.30; 95% CI: 224.78–431.13; PRR: 308.26; chi-square: 11201.91; $p < 0.0001$). Several widely used medications such as bisoprolol, atenolol, and metformin also showed significant, though less pronounced, associations ($p < 0.0001$). The remaining drugs included etanercept, prednisone, rituximab, propranolol, and cyclophosphamide, all of which exhibited significant levels of disproportionate reporting ($p < 0.0001$).

Conclusions

This pharmacovigilance analysis identified multiple medications, spanning different therapeutic classes, that demonstrated a disproportionate association with reports of RPF. Notably, some drugs with well-established safety profiles also emerged as potential signals, warranting increased clinical awareness. While this analysis reveals pharmacovigilance signals suggestive of drug-induced RPF, the observational nature of FAERS data limits causal inference. These findings underscore the need for further clinical research and mechanistic studies to better understand the etiopathogenic role of these agents in RPF development.

Introduction

Retroperitoneal fibrosis (RPF) is a rare but debilitating condition associated with chronic indiscriminate inflammation of the retroperitoneum, often encasing vasculature, muscles and other retroperitoneal structures in fibrous tissue and chronic inflammation[1]. Encasement of the ureters typically results in medial ureteral deviation

and obstructive nephropathy, a serious urological concern that represents the most common disease-related complication of RPF[2,3].

The estimated incidence is 0.1–1.3 cases/100,000 persons per year, with a prevalence of 1.4 cases/100,000 inhabitants, tending to affect more males than females (2:1 in males and 3:1 in females)[4–6]. The mean age at diagnosis is typically between 55 and 60 years.[7]

The clinical presentation of RPF is often non-specific, initially presenting with constitutional symptoms of low-grade fever, malaise and unexplained weight loss. Diagnosis is often delayed and typically occurs only after complications have already developed. RPF-associated complications comprise a range of different clinical manifestations including end-stage renal disease (ESRD), new onset hypertension from renal vasculature impingement, varicocele with chronic testicular pain, vascular issues including lower limb swelling and claudication, and deep vein thrombosis[8–10]. The mainstay of treatment consists of immunosuppressive agents and corticosteroids, while urological intervention is required in more severe cases involving obstructive nephropathy[2].

Largely thought to be idiopathic (> 75% of all cases)[11,12], other etiology for RPF include previous surgery, malignancies, infections, radiotherapy and also certain drugs[13]. A broad range of medications from varying pharmacological classes are thought to be associated with RPF. Ergot alkaloids (e.g. ergotamine, methysergide), dopamine agonists (e.g. pergolide), beta blockers, hydralazine and recently certain anti TNF-a biological agents have been mentioned as potential causes of RPF[14–18], although the evidence supporting these associations remains limited and largely anecdotal for several of these agents. The current scientific evidence dealing with drug-induced RPF is sparse and outdated, and mainly based on single case reports or small case series[19–21] .

In order to fill this knowledge-gap, we aimed here to gather real-life global data to better investigate on the possible association between drugs and RPF. Pharmacovigilance is the pharmaceutical science which focusses on detecting, collecting and monitoring the reported adverse drug reactions (ADRs) in order to identify and respond promptly to possible drug safety issues. The analysis of pharmacovigilance databases, such as the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) provides valuable data when dealing with rare diseases such as RPF. Using the FAERS database, we aimed here to a) identify the range of medications possibly associated with RPF; and b) assess their association signals through disproportionality analysis.

Methods

The FAERS is a safety surveillance program for all drugs and biological agents on the market. The system combines adverse event reports from manufacturers, as mandated by regulations, alongside consumer and healthcare professional reports to create a comprehensive log of potential adverse effects of pharmacological agents[22]. Access to the FAERS database was obtained via the public online search interface[23]. Adverse drug reactions were classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

ADR-related cases were identified using the preferred term (PT) “retroperitoneal fibrosis.” For this study, we recorded the number of individual cases (based on unique case IDs) rather than the total number of ADRs. All drugs associated with at least one RPF case were initially screened; only those linked to ≥ 20 individual cases were arbitrarily included in the disproportionality analysis to ensure statistical stability of estimates and minimize noise from sporadic reports. All reports were already deduplicated by Case ID; no duplicate entries were found. This study

used publicly available, anonymized data from the FDA Adverse Event Reporting System (FAERS). No ethics committee approval or informed consent was required.

Data analysis included variables such as reporter qualification (pharmaceutical company, consumer, or healthcare professional), demographic features (sex and age), ADR severity (e.g., serious, hospitalization, life-threatening, recovery), drug dosages, commercial drug names, and concomitant medications. When available, literature references included in FAERS reports were cross-checked in PubMed/MEDLINE to gather supporting evidence.

Due to the FDA protection of individual privacy, confidential data concerning patients were not accessible.

To assess the strength of the pharmacovigilance signals, we performed a disproportionality analysis by calculating the proportional reporting ratio (PRR), reporting odds ratio (ROR), and their 95% confidence intervals (CI). The PRR was computed using the formula: PRR = (A / (A + B)) / (C / (C + D)), where: A is the number of RPF reports related to the drug of interest, B is the number of non-RPF reports related to the same drug, C is the number of RPF reports related to all other drugs, D is the number of non-RPF reports related to all other drugs[24–26].

Similarly, the ROR was calculated as: ROR = (A / B) / (C / D), with standard error of log(ROR) estimated as √(1/A + 1/B + 1/C + 1/D), and 95% CIs calculated as exp[ln(ROR) ± 1.96 × SE].

To assess statistical significance, chi-square tests were performed and p-values were calculated. A signal was considered significant when PRR > 2, chi-square > 4, and $p < 0.05$. These criteria are commonly used thresholds in signal detection methodology.

All statistical analyses were conducted using SPSS (IBM, Armonk, NY, USA) and Python (v3.10, using SciPy and NumPy libraries).

As FAERS is a spontaneous reporting system, incidence rates cannot be calculated and causal inference cannot be established due to under-reporting, lack of exposure data, and potential confounding by indication.

Results

A total of 1,013 individual cases of retroperitoneal fibrosis (RPF) were identified in the FAERS database between 1969 and March 2025. Of these, 392 (38.7%) were associated with eleven medications, each linked to more than twenty RPF reports, and therefore included in the disproportionality analysis.

The strongest disproportionality signal was observed for methysergide (ROR: 5332.28; 95% CI: 4292.96–6623.21; PRR: 4604.65; chi-square: 429546.30; $p < 0.0001$), followed by pergolide (ROR: 923.85; 95% CI: 686.60–1243.09; PRR: 897.76; chi-square: 40148.64; $p < 0.0001$) and bromocriptine (ROR: 311.30; 95% CI: 224.78–431.13; PRR: 308.26; chi-square: 11201.91; $p < 0.0001$). Other drugs showing statistically significant associations included bisoprolol, atenolol, metformin, etanercept, prednisone, rituximab, propranolol, and cyclophosphamide, all with p-values < 0.0001. All detailed statistical results for the included drugs are reported in Table 1.

Table 1
Drugs associated with more than twenty reports of retroperitoneal fibrosis (RPF) in the FDA Adverse Event Reporting System (FAERS), with corresponding Reporting Odds Ratios (ROR), 95% Confidence Intervals (CI), Proportional Reporting Ratio (PRR), chi-square and p-values.

Drug	RPF Cases	Total Reports (Drug)	% of RPF Reports	ROR	95% CI (ROR)	PRR	Chi-square	p-value
Methysergide Maleate	104	762	10.3%	5332.28	4292.96–6623.21	4604.65	429546.30	< 0.0001
Pergolide	47	1662	4.7%	923.85	686.60–1243.09	897.76	40148.64	< 0.0001
Etanercept	43	592081	4.3%	2.25	1.66–3.06	2.25	28.66	< 0.0001
Bisoprolol	39	33929	3.9%	36.19	26.28–49.86	36.15	1281.77	< 0.0001
Bromocriptine Mesylate	38	3877	3.8%	311.30	224.78–431.13	308.26	11201.91	< 0.0001
Prednisone	35	171358	3.5%	6.37	4.55–8.92	6.37	152.95	< 0.0001
Atenolol	33	26877	3.3%	38.44	27.16–54.39	38.39	1162.62	< 0.0001
Metformin Hydrochloride	33	114620	3.3%	8.98	6.35–12.70	8.98	226.28	< 0.0001
Rituximab	28	196867	2.8%	4.40	3.02–6.41	4.40	71.53	< 0.0001
Propranolol Hydrochloride	27	28620	2.7%	29.34	20.02–43.02	29.32	718.79	< 0.0001
Cyclophosphamide	20	159250	2.0%	3.86	2.48–6.01	3.86	41.52	< 0.0001

Patient age was available for the majority of cases. Of the 392 RPF reports associated with the eleven selected drugs, 216 patients (55.1%) were aged 18–64 years, 100 (25.5%) were aged 65–85 years, 1 case (0.3%) occurred in a patient aged 3–11 years, and age was not specified in 75 cases (19.1%).

RPF was identified in 168 females (42.9%), and 191 males (48.7%), while sex was not specified in 33 cases (8.4%).

The reporter category was available for all recorded cases. The majority of reports were submitted by healthcare professionals (209 cases, 53.3%), followed by consumers (154 reports, 39.3%), with 29 reports (7.4%) from unspecified sources.

Regarding seriousness of the event, 330 out of 392 cases (84.2%) were reported as "serious", while 62 (15.8%) were considered "non-serious". Among the serious cases, 8 deaths (2.0%), 21 patients (5.4%) experienced drug-related disability, and 176 cases (44.9%) required hospitalization.

Discussion

We queried the FAERS dataset to identify drugs most commonly associated with RPF. In our study, ergoline derivatives exhibited the strongest disproportionality signals, in line with their well-established fibrogenic potential and known pathophysiology. Beta-blockers showed moderate signals, reinforcing the need for controlled studies to assess potential class effects. Unexpected associations, such as those observed with metformin and rituximab, merit further investigation. In contrast, signals for agents like prednisone and cyclophosphamide, commonly used in the treatment of RPF, are more likely to reflect confounding by indication rather than a true causal relationship.

To the best of our knowledge, this is the first study to systematically assess the association between pharmacological agents and RPF using the FAERS database from a pharmacovigilance perspective. While previous evidence has mainly relied on isolated case reports or small clinical series focused on individual drugs, our analysis provides a broader and more systematic overview of the key agents implicated in drug-induced RPF. The FAERS database, along with those maintained by European Medicines Agency (EMA) and the World Health Organization's (WHO) Drug Monitoring Programme for International Drug Monitoring (PIDM), represents an important tool for identifying potential safety signals in real-world settings. Although spontaneous reporting systems have well-known limitations, they remain a valuable source of insight, especially when investigating rare ADRs such as RPF.

Current theories suggests that RPF is characterized by fibroinflammatory tissue proliferation in the retroperitoneum, frequently encasing structures such as the ureters, aorta, and inferior vena cava. Its etiology may be idiopathic or secondary to infections, malignancies, or medications. Proposed mechanisms of drug-induced RPF include immune dysregulation, chronic perivascular inflammation, or direct fibroblast stimulation. Some drugs may act through serotonin receptor activation (particularly 5-HT2B), while others may contribute via oxidative stress or cytokine modulation. Our analysis revealed several key findings: as expected, the ergot-derived agents, methysergide, pergolide, and bromocriptine, were associated with the strongest disproportionality signals, reinforcing their established roles in fibrotic disorders. Methysergide, an ergot derivative formerly used for migraine prophylaxis, has long been recognized as a causative agent of fibrotic reactions, including RPF, pleural fibrosis, and cardiac valvulopathy[27]. This serotonergic agonist has been identified in numerous case reports and older pharmacovigilance reviews as a prototypical agent for iatrogenic RPF[28,29], leading to the restriction of its clinical use due to these risks[30,31]. Its fibrogenic effects are thought to stem from its serotonergic activity, particularly through agonism at 5-HT2B receptors, which can stimulate fibroblast proliferation and extracellular matrix deposition[32,33]. In our analysis, methysergide yielded the highest ROR, reinforcing its role as a reference agent for drug-induced RPF. Although the drug is no longer widely used, its presence in the FAERS dataset underlines the strength and persistence of this association.

Pergolide, another ergoline derivative and a dopamine agonist used in Parkinson's disease, shares structural and pharmacodynamic similarities with methysergide. It acts as a 5-HT2B receptor agonist and has been implicated in fibrotic valvulopathy and RPF[34–36]. Its ROR in our study is significantly elevated, confirming prior suspicions. Several case reports and reviews have previously documented RPF in pergolide-treated patients[17,37], and our data substantiate these associations within a larger pharmacovigilance framework.

Etanercept is a tumor necrosis factor (TNF) inhibitor used in autoimmune diseases such as rheumatoid arthritis. Paradoxically, TNF inhibitors have been linked to both improvement and exacerbation of fibrotic diseases. While TNF inhibitors can reduce inflammation, they may also interfere with tissue repair, leading to unintended fibrotic responses in rare cases[38]. A few case reports have associated etanercept with the development of RPF, suggesting immune dysregulation or aberrant wound healing as potential mechanisms[39]. Our analysis indicates a moderate signal of disproportionate reporting, which is statistically significant and warrants further mechanistic exploration.

Bisoprolol, atenolol, and propranolol, three beta-blockers widely prescribed for cardiovascular condition, yielded moderate disproportionality signals in our analysis. This is particularly noteworthy given that beta-blockers have historically been implicated in case reports of RPF, especially when used chronically or in combination with other suspected agents [40,41]. However, no definitive mechanistic explanation has been established, and large-scale epidemiological studies are currently lacking. In our study, bisoprolol and atenolol, both cardioselective β1-adrenergic blockers, showed stronger signals compared to propranolol, a non-selective beta-blocker, which exhibited a slightly weaker association. This pattern may indicate a possible class effect, although the relatively modest ROR values could also reflect the high background exposure to these drugs in the general population.

The pathophysiological rationale remains speculative. Some hypotheses suggest that β-adrenergic blockade could influence fibrotic remodeling through modulation of TGF-β signaling or immune suppression, but conclusive evidence is still lacking[42,43]. Alternatively, the observed signals may be driven by off-target or idiosyncratic reactions, or by shared biases such as frequent co-prescription with other medications associated with RPF. Overall, our findings suggest that beta-blockers may contribute to RPF development in susceptible individuals, but the risk appears to be modest and possibly underrecognized in spontaneous reporting systems.

Bromocriptine is a dopamine agonist used in hyperprolactinemia and Parkinson's disease, structurally similar to ergot derivatives[44]. Its serotonergic activity is weaker, but a class effect among ergot-derived compounds is strongly suspected. It has been associated with pleuropulmonary and retroperitoneal fibrosis in multiple case reports[16,45]. The mechanism is thought to involve serotonergic cross-reactivity, although less potent than in methysergide or pergolide[46]. Our findings reinforce this association, positioning bromocriptine as a well-recognized agent in drug-induced RPF.

Prednisone is a corticosteroid with well-known anti-inflammatory and immunosuppressive effects. Interestingly, it is commonly used in the treatment of RPF rather than being considered a causative agent[13]. However, the modest disproportionality signal observed in our dataset may reflect co-reporting bias or confounding by indication, as prednisone may be co-reported in the management of RPF itself. Thus, this signal likely does not represent a causative relationship but rather reflects a therapeutic use.

Metformin is the first-line therapy for type 2 diabetes mellitus. There is currently no established mechanistic or clinical evidence linking metformin to RPF. Nevertheless, our analysis yielded a significant disproportionality signal. Given its wide use, this unexpected signal could be attributed to confounding factors (e.g., co-administration with other drugs), reporting bias or it may reflect background exposure. However, potential mitochondrial or metabolic effects on fibrogenesis have been postulated in other organ systems, such as the liver, heart, and kidneys, possibly mediated through AMP-activated protein kinase (AMPK) activation[47,48]. Further investigation is needed to clarify this finding.

Rituximab, an anti-CD20 monoclonal antibody used in lymphomas and autoimmune diseases, is not currently recognized as a direct cause of RPF. Boyeva et al. have also evaluated its potential efficacy in idiopathic RPF, particularly due to its role in treating IgG4-related disease[49]. However, a few case reports have described fibrotic complications, possibly resulting from cytokine imbalance or paradoxical immune reconstitution phenomena following B-cell depletion[50,51]. Our finding suggests a statistically significant but weak signal, potentially reflecting confounding by indication in autoimmune conditions already predisposing to RPF, or due to its possible use as a treatment for RPF itself.

Cyclophosphamide is a cytotoxic alkylating agent used in both oncology and immunology. Paradoxically, while it is employed in the treatment of idiopathic RPF due to its ability to suppress inflammation, it may also contribute to fibrotic remodeling by inducing oxidative stress or endothelial damage[52,53]. However, while toxicities such as bladder fibrosis and hemorrhagic cystitis are well documented, its specific role in RPF remains ambiguous[54,55]. Our analysis did not yield a statistically significant signal. However, given its dual role as both treatment and potential contributor to tissue injury, this borderline signal is worth noting.

Taken together, our findings expand the current literature by confirming well-established associations (e.g., ergot derivatives), uncovering novel signals (e.g., metformin), and drawing attention to potentially underrecognized drug classes (e.g., β-blockers). While causality cannot be inferred from spontaneous reporting alone, the strength and consistency of several signals warrant further clinical and mechanistic investigation. Additionally, the possibility of cumulative or synergistic fibrogenic effects in the context of polypharmacy deserves consideration. Many patients receive multiple long-term therapies, which may interact or collectively affect fibrotic pathways, even when individual drug risks are modest. Although FAERS cannot elucidate these dynamics, our findings highlight the need for targeted pharmacoepidemiological studies.

Given the iatrogenic potential of drug-induced RPF, the findings in this study underscore the value of integrating pharmacovigilance with clinical awareness to improve early recognition and prevention of such complications.

Several limitations must be acknowledged when interpreting the results of this study. First, FAERS data are based on voluntary reports submitted by consumers, pharmaceutical companies, or healthcare professionals. As such, the frequency of ADRs cannot be reliably estimated, and causal inferences between drug exposure and adverse events cannot be established [56,57]. An ADR may reflect the clinical manifestation of an underlying disease, an interaction between co-administered medications, or be influenced by other confounding factors not captured in the database[58].

Moreover, the concomitant use of multiple drugs known or suspected to be associated with RPF introduces complexity when attempting to isolate the agent most likely responsible[59].

Reporting bias is also a key limitation. Events already known or publicized are more likely to be reported (notoriety bias), while underreporting of rare conditions like RPF is common due to missed clinical diagnoses or lack of awareness among prescribers [60,61].

From a statistical perspective, disproportionality analyses (such as PRR and ROR) are not designed to quantify clinical risk but rather to detect potential safety signals [62–64]. While we applied standard thresholds for signal detection (e.g., PRR > 2, chi-square > 4, $p < 0.05$), these should be interpreted with caution, particularly in the presence of wide confidence intervals, which reflect small sample sizes for some agents[62].

These findings are best viewed as hypothesis-generating, requiring support from robust clinical studies and mechanistic investigations to validate any true drug–RPF association[65].

Conclusions

This pharmacovigilance analysis identified several medications with a disproportionate reporting of RPF, particularly ergot-derived dopamine agonists such as methysergide, pergolide, and bromocriptine. These findings reinforce previous clinical observations and suggest that, eventually, these associations may reflect a true drug-

induced etiology. Other agents, including beta-blockers, corticosteroids, and antidiabetics, also demonstrated statistically significant, although less pronounced, disproportionality signals.

Considering that drug-induced RPF represents an iatrogenic phenomenon, it is increasingly important that clinicians involved in prescribing are aware of the medications most frequently associated with this rare yet potentially severe condition. Early recognition and drug discontinuation may mitigate irreversible fibrotic damage.

Despite its scale and accessibility, pharmacovigilance data alone are insufficient to establish causality. The limitations inherent to spontaneous reporting systems, including underreporting, lack of exposure data, and incomplete clinical detail, highlight the need for more robust post-marketing surveillance. While disproportionality analysis offers a critical signal detection tool, it should serve as a starting point rather than a conclusion.

Moving forward, these signals must be further explored through well-designed epidemiological studies and mechanistic research. Integrating real-world evidence, clinical registries and experimental data will be key to confirming causal relationships and understanding underlying pathophysiological mechanisms. Pharmacovigilance remains the most effective initial standard for detecting adverse drug reactions at scale, but confirmation requires a coordinated approach across disciplines.

In this context, the present findings aim to contribute to increased clinical awareness and to encourage further investigation into the safety profiles of widely used medications.

Declarations

Notes: Generative AI was used only for language refinement. All content, analyses, and interpretations were produced and verified by the authors. Ethics committee approval was not required and the Helsinki Declaration was not relevant to your study

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The author(s) declare no competing interests.

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Author Contribution

Conception of the work: NS, SB and KF; Data Collection: SB and NS; Data analysis and interpretation: SB, NS and PC; Drafting the article: SB and PC; Critical revision of the article: PC and FD; Final approval of the version to be published: SB, PC, NS and FD

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none

Data Availability

The data that support the findings of this study were derived from the following resources available in the public domain (FDA Adverse Event Reporting System (FAERS) Public Dashboard): [https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis](https:/fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis)

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