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Kharagjitsing, Hardjit; van Eekeren, Rike; van Puijenbroek, Eugène P; van Gelder, Teun; van Bommel, Eric F H

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ORIGINAL ARTICLE

# Retroperitoneal fibrosis and β-blocking agents: Is there an association?

Hardjit Kharagjitsing[1,4] | Rike van Eekeren[2,3] | Eugène P. van Puijenbroek[2,3] | Teun van Gelder[4] | Eric F. H. van Bommel[1]

[1]Department of Internal medicine, Dutch national center of expertise for retroperitoneal fibrosis, Albert Schweitzer hospital, Dordrecht, The Netherlands

[2]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

[3]Department of Pharmacotherapy, epidemiology and economics, Groningen Research Institute of Pharmacy, University of Groningen, The Netherlands

[4]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands

**Correspondence**
Eric F. H. van Bommel, MD PhD, Department of internal medicine, Dutch national center of expertise for retroperitoneal fibrosis, Albert Schweitzer hospital, PO Box 444, 3300 AK, Dordrecht, The Netherlands.
Email: e.f.h.vanbommel@asz.nl

**Aims:** Retroperitoneal fibrosis (RPF) is a rare chronic fibro-inflammatory disorder that may be secondary to certain drugs, including β-blocking agents (BBAs). However, their causative role is unclear. We aimed to investigate this association.

**Methods:** Disproportionality analysis was carried out on cases from 1985 to 4 October 2020 in VigiBase, the World Health Organization pharmacovigilance database. The Bayesian-based $IC_{025}$ metric and reporting odds ratio were used in order to assess the adverse event signal. We also analysed all published case reports from the literature regarding BBA-associated RPF to assess the value of suggested supportive clinical evidence.

**Results:** In total, 1599 individual case safety reports of RPF were reported to VigiBase, of which 132 (32%) concerned 16 different single BBA. For 12 of these agents (75%), reporting of RPF was disproportionate, indicating a potential safety signal. Line listing analysis of individual case safety reports showed no consistent time interval from start of BBA to RPF diagnosis (range 0.7–264 mo). Dechallenge was negative or unknown in the majority of cases (74%). In 18 published cases from the literature, time from start of BBA to RPF diagnosis varied widely (range 3–156 mo). BBA were discontinued 6 months before ($n$ = 1) or at the time of RPF diagnosis ($n$ = 17). Most patients (84%) also received RPF specific treatment. Follow-up duration was short (median 5 mo [range 1–24 mo]) and in most cases (83%) relevant follow-up data were lacking.

**Conclusion:** Although disproportionality analysis indicated a potential safety signal for RPF associated with BBAs, clinical evidence did not support a cause-and-effect relationship.

KEYWORDS
retroperitoneal fibrosis, β-blocking agents, disproportionality analysis|, case reports, spontaneous reporting

## 1 | INTRODUCTION

Retroperitoneal fibrosis (RPF) is a rare disorder of unclear aetiology. It is characterised by chronic nonspecific inflammation of the retroperitoneum leading to fibrosis, which may obstruct the ureters and/or other retroperitoneal structures.[1] The idiopathic form of RPF accounts for >75% of cases. A wide variety of secondary causes have been identified, e.g. neoplasms, infections, trauma, radiotherapy, surgery and the use of certain drugs, of which methysergide has been documented best.[1,2]

The authors confirm that the PI for this paper is E.F.H van Bommel.

  

Among these drugs, several **β-blocking agents** (BBAs) have been implicated as a possible cause of RPF.[1,2] The potential association between use of BBAs and RPF is readily available on the internet. At our tertiary care centre, patients ask if their use of a BBA may have been a causative factor in RPF development and whether or not it should be discontinued. Similar questions arise if we propose to start BBAs in RPF patients for ischaemic heart disease, hypertension or other indication.

Despite multiple publications in the literature, the relationship between the use of BBAs and the occurrence of RPF is still unclear.[1,2] To date, there has not been a critical analysis of available data on this possible association. Using the World Health Organization (WHO) pharmacovigilance database (VigiBase), the world's largest database of individual case safety reports (ICSRs),[3,4] we investigated if there was disproportionate reporting of this possible association. In addition, we searched and scrutinized all published case reports from the literature to date regarding RPF associated with the use of BBAs to assess the value of suggested supportive clinical evidence for this association.

### What is already known about this subject

- Certain drugs may induce development of retroperitoneal fibrosis (RPF).
- There is a long-standing debate as to whether β-blocking agents are capable of inducing RPF development.
- To date, no critical analysis of available data on this possible association has been performed.

### What this study adds

- A potential safety signal for RPF associated with β-blocking agents was generated with disproportionate analysis.
- Further analysis revealed the probable influence of notoriety and protopathic bias on this result.
- The potential safety signal could not be supported by clinical evidence, which fails to document a clear cause and effect relationship.

## 2 | METHODS

### 2.1 | WHO pharmacovigilance database (VigiBase)

### 2.2 | Disproportionality analysis

Utilizing VigiBase, the WHO global database of ICSRs, disproportionality analysis was performed of spontaneously reported cases of RPF with single substance BBAs (data extracted from deduplicated dataset, 4 October 2020). VigiBase is the global database of the WHO Programme for International Drug Monitoring, founded in 1968, in which more than 130 countries participate with their national drug monitoring databases.[3] The database consists of 20 million reports of suspected adverse drug reactions (ADRs), reported to national pharmacovigilance centres.[3] Although these reports have been reported on a voluntary basis and therefore have been subject to reporting biases, information from these database may serve as a first step in detecting drug safety signals. Additional studies from other sources are typically required to confirm the safety signal.

#### 2.2.1 | Drug and ADR coding

In VigiBase drugs are coded according to the WHO drug dictionary, which allows for linking to the Anatomical Therapeutic Chemical (ATC) codes classification system. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA).[5] For extracting a drug-ADR specific association from a database, ATC7 drug code (or ATC4 drug group code) and ADR coding (preferred term, PT) need to be characterised. To retrieve diagnosed ICSRs of RPF with BBAs, we extracted reports of single substance BBA (ATC4 C07A) and PT Retroperitoneal fibrosis. Tables S1 and S2 depict the structure for ATC classification system and MedDRA terminology for ADR in ICSRs, respectively, specifically applied to RPF with BBAs.

#### 2.2.2 | Disproportionate reporting parameters

In spontaneous (or voluntary) reporting of ADRs, disproportionality analysis is a statistical approach for signal generation of possible new and previously undetected ADRs. For this, information component (IC) or the reporting odds ratio (ROR) are determined. IC compares observed and expected values to find associations between drugs and adverse drug reactions using disproportionate Bayesian reporting.[6,7] IC was calculated with the formula: IC = log2 ((Nobserved + 0.5)/(Nexpected + 0.5)), where Nexpected = (Ndrug*Nreaction)/Ntotal; Nexpected: the number of case reports expected for the drug–effect combination; Nobserved: the actual number of case reports for the drug–effect combination; Ndrug: the number of case reports for the drug, regardless of effects; Nreaction: the number of case reports for the effect, regardless of drug. IC025 is the lower end of a 95% credibility interval for the IC. An IC025 value >0 is considered significant and indicates possible signal of detected ADR. ROR is based on case/noncase methodology[6,7]; The ROR of single substance BBAs and RPF was calculated with the formula: ROR = (A*D)/(B*C), where A = observed number of ICSRs of RPF with BBA; B = number of ICSRs of other ADRs with BBA; C = number of ICSRs of RPF with other drugs; D = number of ICSRs of all other drugs with other ADRs in VigiBase. A ROR and lower limit of the 95% confidence interval > 1 is considered statistically significant.

Of note, for signal confirmation, additional information from other sources underpinning a possible causal relationship of the association is necessary.[8,9] For example, information on RPF diagnosis, plausible timing, a pharmacological mechanism and the absence of other explanations help to assess a causal relationship of rare adverse drug reactions.

#### 2.2.3 | Line listing analysis of ICSRs

Relevant and available demographic and clinical information from the ICSRs was exported from Vigibase via the interface of VigiLyze. Extracted variables included age, sex, indication for BBA, concomitant use of cardiovascular- and well known RPF-inducing medication, duration of BBA use to onset of RPF (*latency*), withdrawal of BBA and outcome of the reported reaction, i.e. RPF resolved (*positive dechallenge*) or not resolved (*negative dechallenge*). Information on diagnostics and active RPF specific treatment was not available in this source.

#### 2.2.4 | Reporting rates of ICSRs over time

We also analysed the reporting rates of ICSRs considering RPF with BBAs and with any drug over time. For this, we calculated the ratio of selected reports divided by all reports in the database, per 100 000 and cumulative per year, i.e. the ratio of ICSRs of RPF with any drug; the ratio of ICSRs of RPF with all single substance BBAs (C07A); and the ratio of ICSRs of all single substance BBAs (C07A) with all ADRs.

### 2.3 | Search and review of published case reports from the literature

#### 2.3.1 | Literature search and selection

A literature search in the Medline, Embase, Web of Science, Cochrane CENTRAL and Google Scholar databases was performed for all published articles regarding RPF associated with the use of BBAs. The research team developed the search strategy with help of an information specialist. Full details of our electronic search strategy are depicted in Tables S3 and S4. We searched retroperitoneal, periaortal and periureteral fibrosis, periaortitis and combined that with terms for BBAs or adverse drug reactions to BBAs. The search was performed with thesaurus terms (MeSH and Emtree) and terms in title and abstract, and did not limit the searches to publication type, date or language. Titles and abstracts of all articles were assessed for eligibility before retrieval of full-text versions. We also searched the reference lists of identified articles for further relevant papers. Of note, because of limited availability of identifying data, inherent of pharmacovigilance databases,[3] we were not able to check in VigiBase if published case reports were also reported as ICSR to a national or global database.

#### 2.3.2 | Data extraction

Relevant data were independently extracted from eligible case reports using a set of pre-determined variables by 2 investigators. Data were added and analysed in a separate Microsoft Excel workbook (Microsoft, Redmond, WA, USA). Study variables included: age; sex; medical history; use of specific BBA; use of any other, notably cardiovascular, medication; presence of cardiovascular disease (i.e. hypertension, myocardial infarction, atherosclerosis, peripheral artery disease); length of time on BBA until symptoms development; length of time on BBA until RPF diagnosis; symptoms and signs; presence of hydronephrosis; laboratory findings (i.e. serum creatinine value at presentation and at follow-up [FU]); discontinuation of BBA following RPF diagnosis; specific urological and/or medical treatment of RPF; clinical and radiological outcome of RPF; and FU duration. Reporting all these variables was not a prerequisite for inclusion. If data could not be extracted with confidence, none were entered. Disagreements between investigators were resolved by consensus.

### 2.4 | Statistical analysis

Extracted discrete variables from line listing analysis and from analysis of published case reports from the literature are presented as absolute numbers and proportions (%). Because of skewed distribution of several study variables, extracted continuous variables from line listing analysis and from published case reports in the literature are reported as median and interquartile range (IQR, 25th to 75th percentiles). Analysis of posttreatment serum creatinine vs. creatinine at presentation from published case reports in the literature was performed with the Wilcoxon signed rank-sum test. A 2-sided *P*-value <.05 was considered statistically significant. Calculations were performed with SPSS software, version 15.01 (SPSS Inc., Chicago, Illinois).

## 3 | RESULTS

### 3.1 | Analysis of pharmacovigilance data

At date of extraction, the total number ICSRs in VigiBase was 23 472 137. In total, 1599 ICSRs of RPF have been reported globally to VigiBase, with 410 different suspected drugs since 1968. Of these 410 ICSRs of suspected drug-related RPF, 132 (32%) ICSRs concerned 16 different single substance BBAs. Patient and drug-related characteristics of reported ICSRs of RPF with single substance BBAs and results from disproportionate analysis are shown in Table 1. It should be noted that combination drug products (e.g. metoprolol with hydrochlorothiazide) were excluded for clear overview and because the variety of these combination drugs associated with RPF were very low in number in VigiBase. Twelve single substance BBAs had an $IC_{025}$ > 0 and/or a ROR > 1 for the association with RPF. For 4 other single substance BBAs, the $IC_{025}$ was below zero and, in addition, the ROR could not be calculated because of low number of ICSRs

**TABLE 1** Numbers, patient characteristics and disproportionate reporting parameters of ICSRs of RPF with single substance BBAs from VigiBase

| Characteristic | Median (IQR) or no. (%) | No. of patients with data available (%) | IC/IC025 | ROR (95% CI) |
|---|---|---|---|---|
| Age, y | 61 (52–66) | 116 (88) | | |
| Male sex | 94 (71) | 132 (100) | | |
| BBAs (C07A) | 132* | | 3.3/2.8 | 11.0 (9.2–13.2) |
| Atenolol | 26 | | 3.3/2.7 | 12.2 (8.3–18.0) |
| Propranolol | 26 | | 3.7/3.1 | 16.6 (11.2–24.4) |
| Bisoprolol | 20 | | 3.4/2.7 | 13.6 (8.7–21.2) |
| Metoprolol | 16 | | 2.1/1.3 | 4.7 (2.9–7.8) |
| Timolol | 11 | | 3.2/2.3 | 15.3 (8.5–27.7) |
| Oxprenolol | 6 | | 3.5/2.1 | 65.6 (29.4–146.6) |
| Acebutolol | 5 | | 3.0/1.5 | 29.1 (12.1–70.2) |
| Nadolol | 4 | | 2.7/1.0 | 22.2 (8.3–59.2) |
| Practolol | 3 | | 2.5/0.4 | 22.2 (7.1–68.8) |
| Celiprolol | 3 | | 2.4/0.4 | 20.7 (6.7–64.4) |
| Pindolol | 3 | | 2.6/0.5 | 30.9 (9.9–95.9) |
| Sotalol | 3 | | 1.9/−0.1 | 7.1 (2.3–22.00) |
| Labetalol | 2 | | 0.4/−2.1 | N/A |
| Carvedilol | 2 | | 1.5/−1.0 | N/A |
| Betaxolol | 1 | | 1.2/−2.6 | N/A |
| Nebivolol | 1 | | 0.6/−3.2 | N/A |
| Indication for use | | | | |
| Hypertension | 29 (22) | | | |
| Other cardiac | 9 (7) | | | |
| Other | 1 (1) | | | |
| Unknown | 93 (70) | | | |
| Concomitant medication | | | | |
| Cardiovascular | 56 (42) | | | |
| Ergot alkaloid | 4 (3) | | | |
| Unknown† | 72 (55) | | | |
| Time to RPF diagnosis‡, mo | 35,5 (14–72) | 64 (48) | | |
| BBA discontinued | | | | |
| Yes | 83 (63) | | | |
| No | 6 (4) | | | |
| Unknown | 43 (33) | | | |
| Outcome after cessation of BBA | | | | |
| Dechallenge positive | 22 (26) | | | |
| Dechallenge negative | 33 (40) | | | |
| Unknown | 28 (34) | | | |

ICSRs, individual case safety reports; RPF, retroperitoneal fibrosis; IC information component; ROR, reporting odds ratio; CI, confidence interval; BBA, β-blocking agent; N/A, not applicable. IC025 denotes lower 95% confidence interval of the IC; C07A includes all single substance BBAs (see Table S5).
*: Number of ICSRs with all single substance BBAs;
†: Unknown concomitant medication can indicate both the absence and lack of reporting of other drugs being used concomitantly;
‡: Time interval from start of BBA to RPF diagnosis (*latency*).
Note: for mathematical reasons, the minimum number of ICSRs for ROR calculating is 3.

(Table 1). Available data from the line listing analysis of reported ICSRs in VigiBase show a median age of 61 years with a male predominance. Patients typically used a BBA for hypertension and/or other cardiovascular morbidity (Table 1). In 6 cases, >1 BBA was used, in 4 other cases concomitant use of **ergot alkaloids** was reported. Time from start of BBA to RPF diagnosis (i.e. latency) varied widely with a

range of 3 weeks to up to 264 months (Table 1). In the majority of cases (74%), dechallenge (i.e. outcome of RPF after cessation of the BBA) was negative or unknown (Table 1). In 6 cases (5%), the BBA was continued with reportedly resolution of RPF in 2 of these cases (33%). In all 132 ICSRs, it was unknown if patients received concomitant active RPF treatment. The reporting rates of ICSRs considering RPF with BBAs and with any drug over time are depicted in Figure 1. This analysis shows peaks in reporting of RPF in the 70s and 80s with all drugs. Reporting of any ADR with BBAs shows an increase in the early 80s, which is also the case for ICSRs of RPF with BBAs.

### 3.2 | Analysis of published case reports from the literature

After excluding duplicates and screening for eligibility of 424 initial hits in our electronic search, 31 full-text articles were retrieved for scrutiny (Figure 2). This resulted in 18 case reports for inclusion in this study.[10–27] No additional cases were identified in the manual searches through references. These 18 case reports were published between 1978 and 2017, but predominantly in the last 2 decades of the 20th century (Figure 3). Major characteristics of study patients at presentation are depicted in Table 2. Median age amounted to 51 years with a male predominance. Patients were typically treated with a BBA for hypertension and/or ischaemic cardiac disease. In 6 cases (33%), other antihypertensive agents were used concurrently,[12–14,16,21,25] in 8 cases (44%) comedication was not reported.[15,17–20,22,23,27] In 10 cases (56%), with available information on comedication, concomitant use of methysergide or other ergot alkaloids was not reported.[10–14,16,21,24–26] Except for 1 case with a history of 24 pack-years,[20] smoking history was not reported. The length of time on BBAs before onset of symptoms ranged from 3 to 144 months (median 36 mo; Table 2). In 1 case,[13] the patient developed symptoms 6 months after the BBA was discontinued. Time from start of BBA to definite RPF diagnosis ranged from 3 to 156 months (Table 2). Patients (83%) typically complained of abdominal (50%), back (17%) and/or flank pain (22%), and less frequently of leg and/or scrotal oedema (17%), nausea and vomiting (17%), weight loss (11%), and/or constipation (6%). Most cases (89%) were complicated by hydronephrosis and impaired renal function (Table 2). Major characteristics of treatment and FU are depicted in Table 3. In cases complicated by hydro-ureteronephrosis, (sub)acute urine drainage was typically performed through placing of JJ stents[18,20,21,25] or through placement of an ureterostomy tube.[16] In 1 case, acute temporary haemodialysis was required.[26] FU duration was typically short (Table 3); 1 patient died during admission due to septic shock.[23] The majority of patients (84%) underwent specific surgical (i.e. ureterolysis) and/or medical treatment (i.e. initial high-dose corticosteroids [CSs]) for RPF (Table 3). Post-treatment imaging with intravenous pyelogram, available in 5 cases (28%), all of whom underwent ureterolysis, revealed resolution of ureteric obstruction in 4 cases,[11,17,18,21] and nonfunctioning left kidney with persistent ureteric obstruction in 1 case.[16] Specific FU imaging of the RPF mass was reported in only 3 cases (17%) (Table 3). Apart from discontinuation of the BBA, 2 of these patients were under specific RPF treatment with initial high-dose prednisone (40 mg o.d.).[22,27]

## 4 | DISCUSSION

Certain drugs have been implicated as being capable of inducing RPF development, among them several BBAs.[1,2] Disproportionate reporting of a certain drug–reaction association in a pharmacovigilance database may indicate a potential safety signal. Given

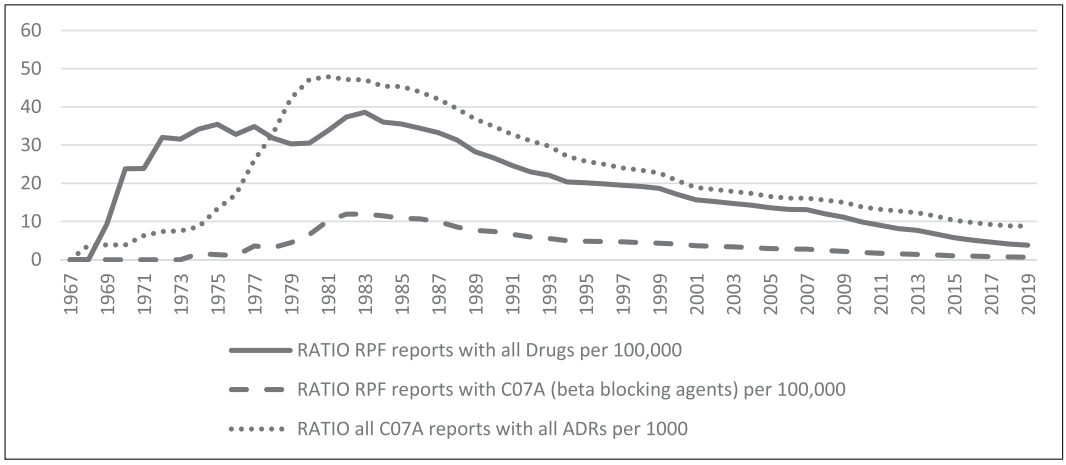


**FIGURE 1** Individual case safety reports (ICSRs) of retroperitoneal fibrosis (RPF) in World Health Organization VigiBase per year. ICSRs of RPF from spontaneous reporting of de-duplicated dataset of World Health Organization VigiBase, extracted on 23 August 2019. Numbers of reports are displayed as ratio of selected reports divided by all reports in the database, per 100 000 and cumulative per year. The ratios of ICSRs of RPF with any drug (*straight line*), and with C07A β-blocking agents (*striped line*) are shown as well as the ICSRs of C07A β-blocking agents (BBAs) in general (*dotted line*). The figure shows peaks in reporting of RPF in the 70s and 80s with all drugs. Reporting of any ADR with BBAs shows an increase in the early 80s, which is also the case for ICSRs of RPF with β-blocking agents

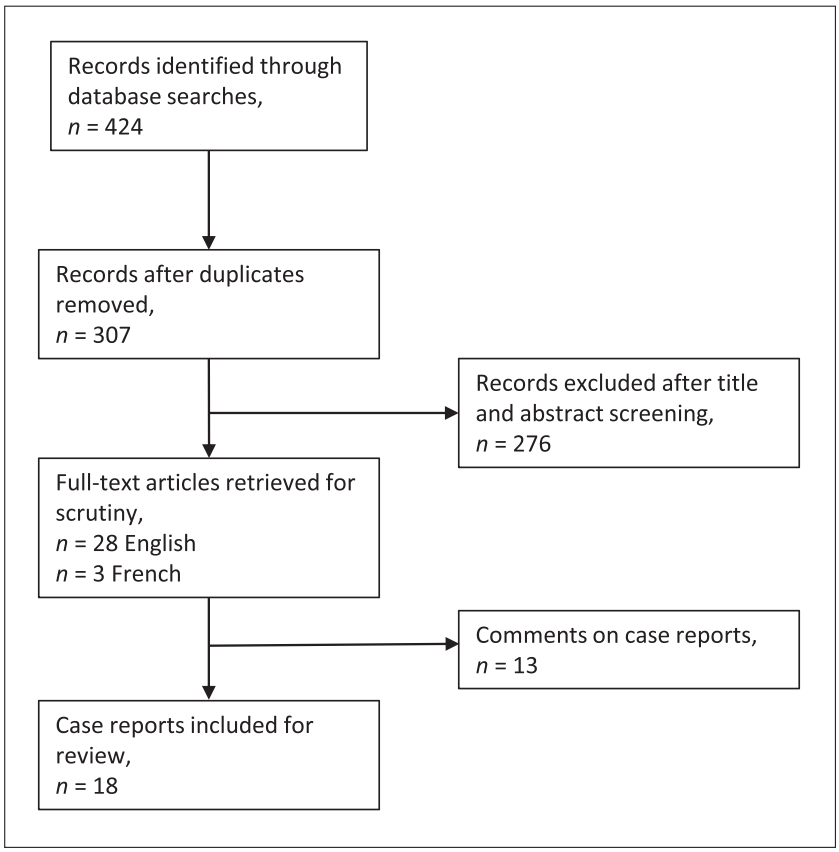


**FIGURE 2** Flow chart of electronic search of the literature

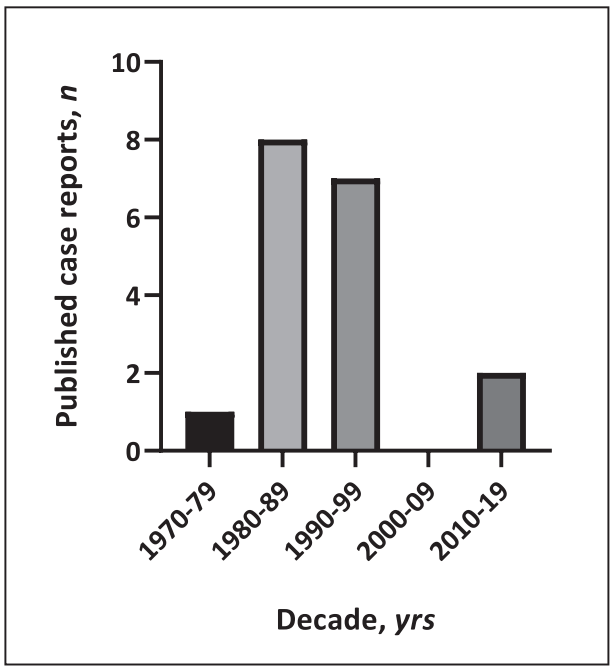


**FIGURE 3** Histogram showing published case reports over time.[10–27] There was predominant reporting of the possible association of retroperitoneal fibrosis with β-blocking agents in the last 2 decades of the 20th century

the nature of these data, however, additional supportive information from other sources on clinical evidence and a plausible biological or pharmacological explanation, are a prerequisite to support an actual causal relationship of the association.[8,9]

In the present study, we observed disproportionate reporting, indicating a potential safety signal, for BBA associated RPF. Although disproportionality analysis is intended to find potential safety signals of ADRs in a large database, it happens that already known ADRs also are disproportionally present in ADR databases, as we noted for methysergide and RPF, which had a very high ROR of 2349.2 (95% confidence interval 2349.9–3559.8; unpublished data).[3] Disproportionality for RPF related associations in VigiBase was high. Since RPF is a rare condition and associated with a limited number of drugs, calculating disproportionality parameters might be skewed.

Some types of biases are likely to have influenced spontaneous ADR reporting of RPF. Misclassification is likely to be based on the assumption that BBAs might induce RPF following the observation in the 70s that practolol was shown to induce sclerosing peritonitis, another chronic fibrotic disorder, which, after safety alerts from both the Committee of Safety of Medicine and from the industry[28] and after >200 cases were reported, was subsequently withdrawn from the market in 1976.[29–31] In the same period and thereafter, several other BBAs were authorised (source KNMP Kennisbank: Pindolol, 1970; Acebutolol, 1973; Sotalol, 1974; Timolol, 1974;

**TABLE 2** Major characteristics of patients from published case reports in the literature

| Characteristic | Median (IQR) or no. (%) | No. of patients with data available (%) | References |
|---|---|---|---|
| Age, y | 51.2 (51.0–57.7) | 18 (100) | 1–18 |
| Male sex | 11 (61) | 18 (100) | 1–18 |
| Beta-blocking agent | | | |
| Atenolol | 4 (22) | | 1,9,11,16 |
| Propranolol | 3 (17) | | 10,14,17 |
| Metoprolol | 3 (17) | | 2,3,18 |
| Nadolol | 2 (11) | | 5,8 |
| Timolol eye drops | 2 (11) | | 4,6 |
| Timolol | 1 (6) | | 15 |
| Sotalol | 1 (6) | | 12 |
| Oxprenolol | 1 (6) | | 13 |
| Unknown | 1 (6) | | 7 |
| Indication for use | | | |
| Hypertension | 10 (56) | | 1–3,8–13,16 |
| Ischaemic heart disease | 5 (28) | | 5,7,14,15,18 |
| Chronic glaucoma | 2 (11) | | 4,6 |
| Unknown | 1 (6) | | 17 |
| Time to RPF diagnosis*, mo | 36 (11–66) | 15 (83) | 1–4,6,9–18 |
| Hydronephrosis | | | |
| Bilateral | 10 (56) | | 3–5,8,9,12,14,15,17,18 |
| Unilateral | 6 (33) | | 1,2,6,10,13,16 |
| No | 1 (6) | | 7 |
| Unknown | 1 (6) | | 11 |
| Creatinine, μmol/L | 279 (151–744) | 12 (67) | 3–6,8,11–15,17,18 |

Abbreviations: IQR: interquartile range (25th to 75th percentile); RPF: retroperitoneal fibrosis.
*: Time interval from start of β-blocking agent to RPF diagnosis (mo).

Metoprolol, 1975; Atenolol, 1975; Bisoprolol, 1986; Celiprolol, 1987) and marketed for cardiovascular diseases. New marketing of drugs is typically associated with increased awareness and surveillance of possible rare side effects. In addition, computed tomography scanning became more readily available in the 1980s, which eased RPF diagnosis and increased awareness of this rare disorder. Indeed, in the present study we found a peak in reporting of ICSRs of RPF with BBAs in the early 80s in VigiBase and most of the possible BBA associated RPF case reports from the literature were also published in the 80s, both reflecting increased awareness of a possible BBA associated fibrotic ADR due to the earlier withdrawal of practolol.[29–31] Hence, results may be influenced by so-called notoriety bias, which describes increased spontaneous reporting after a safety alert und publicity of the event of interest.[32]

From our literature search, we retrieved 18 published cases describing a possible association between the use of BBAs and RPF development. From these published case reports, we could not establish a clear temporal relationship between the use of BBA and RPF development, since median length of time on β-blocking treatment until symptom development amounted to 36 months with a wide range varying from only 3 months up to 144 months. Similarly, line listing analysis of reported ICSRs on RPF with BBAs in VigiBase also showed no consistent time of BBA use to RPF diagnosis but varied widely from only 3 weeks to up to 264 months.

When trying to assess a cause-and-effect relationship, one must take into account the exposure rates of the drug. In the 18 study cases, the BBA was most commonly prescribed for hypertension and/or coronary artery disease. BBAs are widely used in the management of chronic coronary syndromes.[33,34]

This high exposure rate of BBAs was already present in the last decades of the 20th century, as was noted in 1980 for atenolol (350 000 patient-years of exposure) and for propranolol (3 million patient-years of exposure) in the UK.[35] In view of its widespread use, it would certainly not be uncommon for a patient who develops RPF to be on therapy with a BBA without the event being causally related.

Moreover, studies have shown that patients with idiopathic RPF typically have an increased cardiovascular risk profile, often with manifest atherosclerotic vascular disease at the time of RPF diagnosis,[36] further underlining the high probability of use of a BBA, among other cardiovascular agents, by such patients. Present analysis of the 18 study cases revealed that in 33% of cases, other cardiovascular agents were used concurrently. In 1 older study from the 80s

**TABLE 3** Characteristics of treatment and follow-up of patients from published case reports in the literature

| Characteristic | Median (IQR) or no. (%) | No. of patients with data available | References |
|---|---|---|---|
| Treatment characteristics | | | |
| Beta-blocking agent discontinued | | | |
| At diagnosis | 17 (94) | | 1–9,11–18 |
| Before diagnosis | 1 (6) | | 10 |
| Time interval, mo | 6 | | |
| Specific RPF treatment | | | |
| Ureterolysis | 9 (50) | | 4,6,8–13,18 |
| Corticosteroids | 3 (17) | | 3,7,16 |
| Both | 3 (17) | | 14,15,17 |
| Unknown | 3 (17) | | 1,2,5 |
| Follow-up characteristics | | | |
| Clinical recovery* | | | |
| Yes | 13 (72) | | 1–4,6,8,9,11,12,14–17 |
| No | 2 (11) | | 5,7 |
| Unknown | 3 (17) | | 10,11,18 |
| Creatinine, μmol/L | 126 (93–170) | 6 (33) | 4,6,8,13,17,18 |
| Serial imaging RPF mass† | | | |
| Mass regression | 2 (11) | | 6,16 |
| Stable mass | 1 (6) | | 7 |
| Unknown | 15 (83) | | 1–5,8–15,17,18 |
| Duration of follow up, mo | 5.0 (1.8–6.0) | 9 (50) | 1,4,6,12,13,15–18 |

Abbreviations: IQR, interquartile range (25th to 75th percentile); RPF, retroperitoneal fibrosis.
*: As subjectively described by the authors as such in their respective case report;
†: computed tomography-documented follow-up of RPF mass.

focussing on drug use and blood pressure in a large group of RPF patients in the UK, 64% of patients were hypertensive at the time of diagnosis.[37] Among a variety of antihypertensive drugs, 7% of patients with a positive drug history before RPF diagnosis used a BBA, while after RPF diagnosis, 24% of patients were started on treatment with a BBA, among several other antihypertensive drugs.

The high prevalence of hypertension in patients with RPF can be explained by several causes. It may be pre-existent, often long-standing, as primary hypertension or may be secondary due to atherosclerotic renal damage.[1,36] In the acute phase of extrinsic urinary tract obstruction in patients with RPF, hypertension may develop through a sharp rise in renin level. In the longer term, hypertension may occur or persist due to chronic obstructive nephropathy.[38] Although rare, hypertension may result from entrapment of the renal artery by the RPF mass.[1] Hence, it is likely that RPF is either an incidental finding in patients taking BBAs or that acute or chronic hypertension occurs secondary to extrinsic urinary tract obstruction caused by RPF and that BBAs were used to treat this hypertension. All this suggests that the disproportionate reporting may in part be due to so-called protopathic bias, which describes the use of a drug for symptoms with (at that point) an undiagnosed disease, that later on is presented as an ADR.[39]

For assessing a possible cause and effect relationship, it is also a prerequisite to observe the course of the observed adverse effect (i.e. RPF) after cessation of the particular drug (i.e. BBA). Although BBAs were typically discontinued at the time of RPF diagnosis in published cases from the literature, evaluation of the natural disease course after cessation of BBA was precluded for several reasons. In particular, specific therapy for RPF, i.e. long-term initial high dose CSs was given and/or ureterolysis was performed in the majority of published cases from the literature. CSs are known to induce RPF mass regression and with ureterolysis, surgical resolution of ureteric obstruction is achieved.[1] In addition, objective FU data were absent in the majority of published cases, and in 2 of 3 published cases in which radiological FU data were available, specific treatment with initial high-dose CSs was prescribed. Line listing analyses of ICSRs on RPF and BBAs in VigiBase also revealed that, in many of these cases, RPF did not resolve after cessation of the BBA. In addition, in 4 cases, ergot alkaloids that are known to cause RPF were used concomitantly. Moreover, information of active RPF treatment and the exclusion of other causes of RPF was lacking in this set of ICSRs.

A plausible pathophysiological explanation of the presumed drug-induced adverse effect (i.e. BBA induced chronic retroperitoneal fibro-inflammatory reaction), if available, would strengthen a possible cause–effect relationship. For RPF and BBAs several hypotheses have been postulated. One hypothesized mechanism is that BBAs may induce fibro-inflammatory changes by interfering with the regulating role of endogenous catecholamines, since these reduce lysosomal

leakage from phagocytes, inhibiting inflammatory tissue damage.[40] Other proposed hypotheses suggest that BBAs lead to the production of collagen by the release from normal endogenous β-blocking agonistic suppression of the production of collagen, or that BBAs decrease the ratio of adenosine 3:5-cyclic monophosphate to cyclic glucose monophosphate, leading to an increase in cellular proliferation.[24] Also a fibrotic reaction as a consequence of a drug allergy or as a pure pharmacological action of BBAs has been suggested.[26] These varying and largely theoretical hypotheses for a possible association of BBA induced RPF are not convincing and from these various hypotheses, no uniform pathophysiological explanation could be derived which could explain a group effect for BBA induced RPF. In addition, these hypotheses are not substantiated by supportive experimental evidence. On the contrary, recent experimental studies suggest that BBAs may even have anti-fibrotic properties.[41–43] Moreover, the practolol-associated fibrotic reaction has shown to be a specific drug effect and not a class effect of BBAs.[29]

All this is in sharp contrast to the evidence supporting a causal relation between methysergide and RPF development. An increased risk of developing RPF in patients treated with methysergide was observed compared to that in the general population (1 per 100 *vs* 1.3 per 100 000 patients),[36,44] with a clear temporal relationship between its use and RPF development. In addition, clinical and radiologically-documented regression of RPF after cessation of methysergide, without any other intervention, was observed.[44] Fibrotic reactions are believed to be associated with persistent agonist activation of the 5-$HT_{2B}$ receptor and long-term treatment with methysergide will expose patients to the potential for tissue fibrosis mediated by its principal active metabolite, methylergometrine.[45] In recent years, RPF development by other ergot derivatives is also observed and fibrosis seemed to be a class effect of ergot-derived dopamine agonists.[46]

Inherent of all pharmacovigilance studies using spontaneous reports, specific data on the number of patients exposed to BBAs are lacking. This precludes the possibility of calculating the absolute frequency of RPF on the basis of ICSRs, notably because of underreporting.[9,47] In addition, data collection differs from 1 country to another for legislative and regulatory reasons. However, widespread underreporting would not affect the results of this kind of study and underreporting is typically similar for all drugs within a given class.[5,9,47] In addition, pharmacovigilance databases are designed to detect signals rather than to exhaustively record all ADRs.[47] Conversely, we studied the world's largest pharmacovigilance database in which >130 countries participate. Hence, data were exhaustive and reflected *real-life* medication use. In addition, we used a validated method of investigating disproportionality between reports and drugs.[6,7] Moreover, we scrutinized the literature to assess if the potential signal could be supported by clinical evidence. Of note, based on the information from case reports alone the existence of a potential relationship can be suggested but not be quantified. To do so, additional pharmacoepidemiological studies are needed but, given the rarity of RPF and the type of drugs, are difficult to perform. A case–control study might be a suitable alternative, although such study would be hampered by the inclusion of a wide variety of BBAs. In addition, results from the present study do not readily point towards performing such study.

## 5 | CONCLUSION

Although disproportionality analysis indicated a potential safety signal for RPF associated with BBAs, our study could not support this finding by clinical evidence, which fails to document a clear cause and effect relationship. In addition, calculating disproportionality parameters may be skewed and results are probably influenced by notoriety as well as by protopathic bias. There is also no clear pathophysiological explanation for the presumed BBA induced fibrotic reaction.

The high exposure rate of BBAs in the general population and the likelihood of RPF patients to have pre-existent or concurrent hypertension implicate that it would certainly not be uncommon for an RPF patient to use a BBA, among other cardiovascular drugs. RPF is therefore probably either an incidental finding in patients taking BBAs or hypertension occurs secondary to extrinsic urinary tract obstruction caused by RPF and BBAs are used to treat this hypertension.

### 5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).

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The pharmacovigilance data are obtained from VigiBase, the WHO global database of ICSRs. These reports come from various sources and the probability of suspected adverse effect being drug related is not the same in all cases. This article does not necessarily represent the opinion of UMC or WHO. The authors wish to thank W.M. Bramer, biomedical information specialist from the Erasmus MC Medical Library for his valuable help in the literature search strategy.

#### COMPETING INTERESTS

The authors have no COI to declare.

#### CONTRIBUTORS

H.K.: acquisition, analysis and interpretation of data, principal writer of the manuscript; R.v.E.: acquisition, analysis and interpretation of data, co-writer of the manuscript; E.P.v.P.: contributed to analysis and interpretation of data. Revised the manuscript critically for important intellectual content; T.v.G.: involved in conception and design of the study. Revised the manuscript critically for important intellectual content; E.F.H.v.B.: conception and design of the study, analysis and interpretation of data. Involved in drafting the manuscript and revising

it critically for important intellectual content. All authors provided critical feedback and helped shape the research, analysis and manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Eric F. H. van Bommel* https://orcid.org/0000-0002-9803-1715

## REFERENCES


1. van Bommel EF. Retroperitoneal fibrosis. *Neth J Med*. 2002;60(6):231-242.
2. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet*. 2006;367(9506):241-251.
3. Uppsala Monitoring Centre. VigiBase® [Internet]. Uppsala (Sweden); [cited 2020 Mar 10]. Available from: https://www.who-umc.org/vigibase/vigibase/
4. World Health Organization. The Importance of Pharmacovigilance - Safety Monitoring of medicinal products [Internet]. United Kingdom; 2002 [cited 2020 Mar 10]. 52 p. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. ISBN: 92 4 159015 7.
5. Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts. *Drug Inf J*. 2008;42(5):409-419. (1), and the UMC webpage for more updated information. *Drug Information Journal*. 2008
6. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJ, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. *Clin Pharmacol Ther*. 2007;82(2):157-166.
7. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf*. 2002;11(1):3-10.
8. Hauben M, Aronson JK. Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Saf*. 2009;32(2):99-110.
9. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br J Clin Pharmacol*. 2011;72(6):905-908.
10. Doherty CC, McGeown MG, Donaldson RA. Retroperitoneal fibrosis after treatment with atenolol. *Br Med J*. 1978;2(6154):1786.
11. Jonhson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol. *Br Med J*. 1980;280(6217):864.
12. McCluskey DR, Donaldson RA, McGeown MG. Oxprenolol and retroperitoneal fibrosis. *Br Med J*. 1980;281(6253):1459-1460.
13. Henri L, Groleau M. Retroperitoneal fibrosis after treatment with propranolol. *Drug Intell Clin Pharm*. 1981;15:696.
14. Pierce JR Jr, Trostle DC, Warner JJ. Propranolol and retroperitoneal fibrosis. *Ann Intern Med*. 1981;95(2):244.
15. Laakso M, Arvala I, Tervonen S, Sotarauta M. Retroperitoneal fibrosis associated with sotalol. *Br Med J (Clin Res Ed)*. 1982;285(6348):1085-1086.
16. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. *Br Med J (Clin Res Ed)*. 1982;284(6309):83-84.
17. Rimmer E, Richens A, Forster ME, Rees RW. Retroperitoneal fibrosis associated with timolol. *Lancet*. 1983;1:300.
18. Benitah E, Chatelain C, Cohen F, Herman D. Retroperitoneal fibrosis: a systemic effect of beta-blocker eyedrops? *Presse Med*. 1987;16:400-401.
19. Ahmad S. Atenolol and retroperitoneal fibrosis. *South Med J*. 1990;83(11):1367.
20. Ahsan N, Choudhury AA, Berger A. Retroperitoneal fibrosis. *Am Fam Physician*. 1990;41(6):1775-1780.
21. Delorme E, Vial T, Rabilloud M, de Carlan H, Evreux JC. Retroperitoneal fibrosis with eye-drops containing timolol. *J Urol*. 1990;96:449-451.
22. Sebban C, Lederlin P, Guerci A, et al. Retroperitoneal fibrosis due to beta-adrenergic receptor blocking agents? Case report and review of the literature. *La Rev Med Interne*. 1993;14(6):612.
23. Cappell MS. Obstructive jaundice due to retroperitoneal fibrosis involving the head of the pancreas. *J Clin Gastroenterol*. 1994;18(1):53-56.
24. Ahmad S. Association of metoprolol and retroperitoneal fibrosis. *Am Heart J*. 1996;131(1):202-203.
25. Demko TM, Diamond JR, Groff J. Obstructive nephropathy as a result of retroperitoneal fibrosis: a review of its pathogenesis and associations. *J am Soc Nephrol: JASN*. 1997;8(4):684-688.
26. Shirani M, Davoudian A, Sharifi A. Retroperitoneal fibrosis associated with propranolol: a case report; is corticosteroid administration necessary after ureterolysis? *J Renal Inj Prev*. 2013;2(2):67-69.
27. Demirdal D, Fitzgerald G, Gunnane G. Challenges in retroperitoneal fibrosis: A case series. *Rheumatology*. 2017;56:ii57.
28. Editorial: side effects of practolol. *Br Med J*. 1975;2:577-578.
29. United Nations - Department of Economic and Social Affairs. Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments. Pharmaceuticals 8th Issue. New York. c2003. ISBN: 92-1-130230-7. Sales no. E03IV.9.
30. Brown P, Baddeley H, Read AE, Davies JD, McGarry J. Sclerosing peritonitis, an unusual reaction to a beta-adrenergic-blocking drug (practolol). *Lancet*. 1974;2(7895):1477-1481.
31. Mann RD. An instructive example of a long-latency adverse drug reaction--sclerosing peritonitis due to practolol. *Pharmacoepidemiol Drug Saf*. 2007;16(11):1211-1216.
32. van Hunsel F, van Puijenbroek E, de Jong-van den Berg L, van Grootheest K. Media attention and the influence on the reporting odds ratio in disproportionality analysis: an example of patient reporting of statins. *Pharmacoepidemiol Drug Saf*. 2010;19(1):26-32.
33. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;41:407-477.
34. GIP/Zorginstituut Nederland [database on the Internet]. Amsterdam (Netherlands). 2004 - [updated 2019 Oct 3; cited 2020 Mar 10]. Available from: https://www.gipdatabank.nl/
35. Castle WM, Cruickshank JM, Waycott JA. Retroperitoneal fibrosis associated with atenolol. *Br Med J*. 1980;281:311.
36. van Bommel EF, Jansen I, Hendriksz TR, Aarnoudse AL. Idiopathic retroperitoneal fibrosis: prospective evaluation of incidence and clinicoradiologic presentation. *Medicine*. 2009;88(4):193-201.
37. Pryor JP, Castle WM, Dukes DC, Smith JC, Watson ME, Williams JL. Do Beta-Adrenoceptor Blocking-Drugs Cause Retroperitoneal Fibrosis. *Br Med J*. 1983;287(6393):639-641.
38. Martinez-Maldonado M, Kumjian DA. Acute renal failure due to urinary tract obstruction. *Med Clin North Am*. 1990;74(4):919-932.
39. Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. *BMC Med Res Methodol*. 2019;19(1):53.
40. Marshall AJ, Baddeley H, Barritt DW, et al. Practolol peritonitis. A study of 16 cases and a survey of small bowel function in patients taking beta adrenergic blockers. *Q J Med*. 1977;46(181):135-149.
41. Hamdy N, El-Demerdash E. New therapeutic aspect for carvedilol: antifibrotic effects of carvedilol in chronic carbon tetrachloride-induced liver damage. *Toxicol Appl Pharmacol*. 2012;261(3):292-299.

42. Kobayashi M, Machida N, Mitsuishi M, Yamane Y. Beta-blocker improves survival, left ventricular function, and myocardial remodeling in hypertensive rats with diastolic heart failure. *Am J Hypertens*. 2004;17(12):1112-1119.
43. Strack I, Schulte S, Varnholt H, et al. beta-Adrenoceptor blockade in sclerosing cholangitis of Mdr2 knockout mice: antifibrotic effects in a model of nonsinusoidal fibrosis. *Lab Invest*. 2011;91(2):252-261.
44. Graham JR, Suby HI, LeCompte PR, Sadowsky NL. Fibrotic disorders associated with methysergide therapy for headache. *N Engl J Med*. 1966;274(7):359-368.
45. European Medicines Agency, Committee for Medicinal Products for Human Use. Assessment report - Restrictions on the use of methysergide-containing medicines. London. 2014 Feb 20. 19 p. Procedure No. EMEA/H/A-31/1335.
46. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Ther*. 2006;28(8):1065-1078.
47. Harmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. *Eur J Clin Pharmacol*. 2008;64(8):743-752.

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