EXPERT OPINION

Drug-induced atrial fibrillation

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Introduction: Atrial fibrillation (AF) is the most common arrhythmia and an important cause of hospitalization, morbidity, and mortality. A myriad of drugs can induce AF. However, drug-induced AF (DIAF) receives little attention. Thus, this review is an attempt to attract the attention on this adverse effect.
Areas covered: Published reports of drug-induced AF (DIAF) are reviewed in this paper, from January 1974 to December 2011, using the PubMed/Medline database and lateral references.
Expert opinion: In most cases, DIAF is paroxysmal and terminates spontaneously, but sometimes AF persists and it is necessary to perform a cardioversion to restore sinus rhythm and avoid progression to persistent AF. Because of the short duration of DIAF, in addition to physicians/patients not being knowledgeable about this side effect, the real incidence and clinical consequences of DIAF are presently unknown. DIAF is an increasing problem, as some widely prescribed drugs can present this adverse effect. The risk is expected to increase in the elderly and in patients with comorbidities. It is important that physicians understand the significance of DIAF, to increase the collaboration between cardiac and non-cardiac professionals, and to educate patients to make them aware of this adverse side effect.

Keywords: arrhythmia, atrial fibrillation, drug-induced, side effect

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1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances [1,2]. Its prevalence increases with age (from < 1% at 50 – 60 years, to 5 – 15% at 80 years or older) and is associated with increased cardiovascular morbidity and mortality. AF increases risk throughout the cardiovascular continuum, as it is associated with a nearly doubled risk of death and an almost five-fold increase in the risk of stroke compared to patients in sinus rhythm [1,2]. Although AF can occur in apparently healthy individuals, more than 70% of patients with AF present structural heart diseases (i.e., hypertension, cardiac hypertrophy, coronary artery disease, heart failure, valvular diseases, myocardiopathies) or noncardiac diseases (diabetes mellitus, hyperthyroidism, obesity, obstructive sleep apnea, and pulmonary diseases) [1,2]. Acute temporary causes of AF include excessive alcohol intake, surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, and drugs. Drug-induced AF (DIAF) is a topic that has not received much attention by both cardiac and noncardiac professionals and is almost absent in the literature. However, DIAF can be clinically relevant, particularly in polymedicated elderly patients, as they present a high incidence of AF, and in patients treated with certain cardiovascular or noncardiovascular drugs [3]. In this article, we review the therapeutic drugs that can produce AF and the potential mechanisms involved in DIAF (**Tables 1,2,3,4**). Case reports of DIAF are presented as Supplemental Material (**Table 5**).

2. Methods

We reviewed published reports on DIAF in English from January 1974 to December 2011 using the Medline database using PubMed and lateral references. We used the

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Article highlights.

- A myriad of cardiovascular and non-cardiovascular drugs can modify atrial electrophysiological and structural properties as well as cardiac autonomic tone and induce AF. These drugs should be recognized as a potential cause of AF, particularly in the elderly and in patients with comorbidities associated with AF.
- The overall incidence of DIAF is unknown, but with a few exceptions, it is likely very low, and there is no clear evidence on whether DIAF can increase the risk of thromboembolism or mortality.
- It is important to determine whether the episode of AF is related to the administration of a given drug.
- The onset of DIAF is quite variable and risk factors for DIAF have not been characterized.
- Treatment of DIAF is not different from that recommended for paroxysmal AF. However, the effectiveness of rhythm- and rate-control therapies on DIAF has been adequately studied as DIAF very rarely last for more than 48 h. Furthermore, randomized trials upon which guidelines are based, predominantly excluded patients with cancer, renal and pulmonary diseases.
- Patients treated with drugs that can cause AF should be informed that the medication, on rare occasions, can increase heart rate and produce palpitations, dizziness, light-headedness, shortness of breath or chest pain. If this occurs, they should contact their physician immediately.

This box summarizes key points contained in the article.

subject heading "atrial fibrillation" combined with the terms "drug-induced," "chemically-induced," "associated with drug," and "as side effect." Reports describing a weak association between drug administration and AF or dealing with supraventricular tachycardias or atrial flutter were excluded.

3. Atrial fibrillation: electrophysiological mechanisms

The initiation and maintenance of AF requires a trigger for initiation (usually a premature ectopic beat) and a favorable substrate produced by electrical and structural remodeling for maintenance [1,2,4,5]. With respect to AF, available data support a "focal" mechanism involving automaticity or multiple reentrant wavelets [1,2]. Both mechanisms are not mutually exclusive and are likely to coexist at various times. Cellular mechanisms of focal activity might involve both triggered activity (originating within or near the pulmonary veins, atria, or both) and reentry [5]. Indeed, paroxysmal AF, the main type of DIAF, usually involves a driver in the cardiac muscle sleeves, around one or more pulmonary veins [6]. According to the multiple wavelet hypothesis, AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. As long as the number of wavefronts does not decline below a critical level, the multiple wavelets will sustain the arrhythmia [1,2]. The maintenance of continuous activity in re-entrant models depends on the balance between atrial excitability and atrial effective refractory period (AERP). The number of coexisting atrial wavelets is determined by the atrial mass and the *wavelength* (WL = conduction velocity x AERP) of the atrial impulse. Slow conduction and short AERP together with a large atrial mass increase the number of wavelets and the likelihood of continuous conduction in a potential reentry pathway. AF induces electrophysiological [shortens atrial action potential duration (AAPD) and AERP] and structural changes (dilatation, hypertrophy, fibrosis, and inflammation) that facilitate its perpetuation. These structural changes, which can also result from coexisting structural heart diseases associated with AF as well as from aging, or produced by some drugs (**Table 4**), create a stable arrhythmogenic substrate that facilitates the perpetuation of AF.

Fluctuations in autonomic tone precede the development of paroxysmal AF, with a primary increase in sympathetic tone followed by an abrupt shift toward vagal predominance [7]. Catecholamines enhance automaticity and promote triggered activity (early and delayed afterdepolarizations) in the pulmonary veins, while acetylcholine abolishes atrial automaticity. Furthermore, both sympathetic and parasympathetic stimulation produce a heterogeneous shortening of AAPD and AERP, which confirms that fluctuations in autonomic tone can facilitate the induction and/or maintenance of AF.

Multiple mechanisms have been proposed to explain DIAF, including (**Table 4**) a direct effect on atrial electrophysiological properties (leading to an increase in focal activity originating from pulmonary veins and/or atria, slow atrial conduction velocity and/or short AAPD and AERP), direct myocardial damage (including hypertrophy, fibrosis, heart failure, ischemia, abnormalities in Ca^{2+} handling, myocarditis, pericarditis), changes in cardiac autonomic tone (increased sympathetic or parasympathetic tone), release of proinflammatory cytokines, increase in oxidative stress, hypotension or electrolyte disturbances. Finally, it is possible that some patients may present a trigger (i.e., premature atrial beats) that can induce DIAF when a given drug produces changes (remodeling) in atrial electrophysiological and structural properties. This latter possibility is particularly possible with chemotherapy agents and can be accentuated in patients with other comorbidities that produce atrial remodeling and increase the risk of AF (i.e., hypertension, heart failure, valvular disease or coronary artery disease).

In this review, the possible mechanisms involved in DIAF will be discussed in each section.

4. Drug-induced AF (DIAF)

4.1 Anti-inflammatory drugs

Two nested case-control analyses find that use of glucocorticoids, nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors is associated with an increased

Table 1. Atrial fibrillation induced by anti-inflammatory drugs, respiratory medications in the treatment of COPD and asthma and bisphosphonates.

Drug* [Ref.]	Population	Relative risk (95% confidence intervals) of AF
Nonsteroidal anti-inflammatory agents (NSAIDs) [8,9]	1034 AF cases, 5000 controls 32602 cases, 325918 controls	1.44 (1.08-1.91) Non-selective: 1.33 (1.26-1.41) COX-2 inhibitors: 1.50 (1.42-1.59)
Steroidal anti-inflammatory agents [8,11]	1034 AF cases, 5000 controls 20221 AF cases, 202130 controls	2.49 (1.56-3.97) 1.92 (1,79-2,02)
High-dose (pulse) glucocorticoid therapy [10,11]	385 cases, 6364 controls 202130 cases, 20221 cases	6.07 (3.90-9.42) 1.92 (1.79-2.06)
Respiratory medications [12]	710 cases, 5000 controls	Inhaled steroids: 1.1 (0.9-1.3) Oral steroids 2.7 (1.9-3.8) Beta-agonists 1.3 (1.0-1.8) Antimuscarinics 1.2 (0.9-1.5) Teophyllines: 1.8 (0.9-3.7)
Alendronate [160,163,165]	6459, postmenopausal women 719 female AF cases, 1057 controls 15795 fracture patients, 31590 controls	1.51 (0.97-2.40) 1.86 (1.09-3.15) Aledronate: 1.30 (1.14-1.48) Etidronate: 1.08 (0.94-1.24)
Zoledronic acid [159]	3889 postmenopausal women	1.51 (0.97 to 2.40)

*Drugs are listed alphabetically.

COPD: Chronic obstructive pulmonary disease; COX-2: Cyclooxygenase-2; OR: Odds ratio; PAF: Paroxysmal AF; SVT: Supraventricular tachycardia.

Table 2. Atrial fibrillation induced by cardiovascular drugs.

Drug* [Ref.]	n, Clinical history	Incidence (%) of atrial fibrillation
Acetylcholine (intracoronary) [144]	1000	17.1 %
Adenosine during EPS [51-53]	200	12%
	229 with SVT	15% in AVRT, 11% in atrial tachycardia and 17% with PRJT
	198	0.4%
Dobutamine for stress echocardiography [22-31]	100	1%
	1118	0.6 %
	650	1.2%
	1012	1.2%
	2574	1.1%
	1035	1.6%
	3800	2%
	6755	0.4%
	179, ≥ 70 years old	1.1%
	227, ≥ 70 years old	3%
Dobutamine [34,39]	144, after coronary revascularization	7.6%
	663 with ADHF	6.1%
Dopamine (renal dose) [21]	1,731 after cardiac surgery	23.3% (14.1% in untreated patients)
Dopexamine [20]	Data on file	1.4%
Enoximone [34]	**72 after oronary revascularization**	8.3%
Flecainide [41]	**227 with PAF**	1.3%
Levosimendan [39]	**664 with ADHF**	9.1%
Milrinone [33,35,36]	951 with ADHF	4.6%
	239, after cardiac surgery	28.9%
	120, dobutamine vs milrinone after cardiac surgery	18% with dobutamine, 5% with milrinone
Verapamil [45,47,48]	35 with PAF	Enhances sustenance of AF
	40 with HCM	5%
	30 with paroxysmal SVT	20%

*Drugs are listed alphabetically.

AADs: Antiarrhythmic drugs; ADHF: Acute decompensated heart failure; AVRT: Atrioventricular reentry tachycardia; EPS: Electrophysiological study; PAF: Paroxysmal AF; PRJT: Permanent junctional reciprocating tachycardia; SVT: Supraventricular tachycardia.

Table 3. Atrial fibrillation induced by cancer chemotherapy.

Drug* [Ref.]	n, Clinical history	Incidence (%)
Amsacrine [110]	5340	3.6%
Cisplatin, intrapericardially [80-82]	25	12%
	46	15.2%
	44	32%
Cyclophosphamide [85]	45	2.2%
Doxorrubicin [71,72]	256	2.2%
	29	10.3%
"Eight-drugs-in-one-day" chemotherapy [196]	31	9.6%
5-fluorouracil [93]	644	0.93%
5-FU and cisplatin [94,95]	76	6.5%
	72	4.2%
Gemcitabine ± vinorelbine [97]	49 with NSCL	8.2% (AF or flutter)
Ifosfamide (Phase I) [84]	52	10%
Interleukin-2 [105-108]	157 (180 courses)	13.3% (AF or SVT)
	317 (423 courses)	8% of courses produce AF
	47	4.3%
	93 (114 courses)	4.3%
Melphalan high-dose prior to bone marrow	76	6.6%
transplant [86-90]	58 (Phase I)	8.3%
	438	8%
	34, over 65 y	11.7%
	40, over 60 y	22.5%
Taxol [91]	3.400	0.18%

*Drugs are listed alphabetically.
AF: atrial fibrillation. SVT: supraventricular tachycardia.

risk of AF (**Table 1**). This association is strongest for new users [8,9].

High-dose (pulse) corticosteroid therapy increases the risk of AF in case-control studies (**Table 1**). In the Rotterdam Study, high-dose (but not low-/intermediate-dose) glucocorticoid use is associated with an increased risk of AF compared with non-users [10]. The association is stronger among new users, but is independent of the indication for corticosteroid therapy. In another Danish study, current glucocorticoid use is associated with an almost two-fold increased risk of AF or flutter compared with never use in patients with and without chronic obstructive pulmonary disease (COPD) or asthma and cardiovascular diseases [11]. Again, the risk is four times higher among new glucocorticoid users. In patients with asthma and COPD of the UK General Practice Research database, oral glucocorticoids are associated with an increased risk of AF, even after adjustment for comorbidity [12]. Long-term glucocorticoid use is associated with risk factors for AF, including diabetes mellitus, hypertension, heart failure, and ischemic heart disease. Several mechanisms have been proposed to explain AF after pulse methylprednisolone: i) a direct increase in K^+ efflux which, in turn, influences arrhythmogenesis; ii) a mineralcorticosteroid effect leading to retention of sodium and fluid, which may cause hypertension, left atrial enlargement, and congestive heart failure—all known risk factors for AF; iii) a rapid neuroendocrine imbalance; and iv) the development of late potentials and, occasionally, a marked peripheral vasodilatatory response [3,10-13]. The highest risk of AF among new users of glucocorticoids suggests either a short-term adverse effect (e.g., development of hypertension within a few days after initiation of therapy) or an effect associated with the severity of the underlying disease (e.g., inflammation) [11]. There are case reports of AF after high-dose (pulse) methylprednisolone therapy in patients with different pathologies and after administration of fluticasone propionate; in one patient, AF reoccurred with methylprednisolone treatment but not after fluocortolone (**Table 5**) [14-18].

4.2 Cardiovascular drugs

4.2.1 Diuretics

Thiazides can cause hypokalemia that induces atrial ectopic activity and shortens AAPD, providing the electrophysiological basis for induction of AF. Three hypertensive patients on long-term chlorthalidone therapy develop AF and hypokalemia that reverses to sinus rhythm after normalizing the kalemia (**Table 5**) [19].

4.2.2 Positive inotropic agents (Table 2)

Dopamine, dobutamine, and dopexamine can produce AF in patients with acute decompensated heart failure and increase the risk of postoperative AF when given after open-heart surgery in hypotensive patients [20-22]. In patients undergoing coronary artery bypass grafting, the incidence of paroxysmal AF is greater in patients receiving renal-dose dopamine [21]. AF occurs in 0.4 – 2% of patients undergoing dobutamine stress echocardiography, a noninvasive test to assess coronary

Table 4. Mechanisms involved in drug-induced atrial fibrillation.

Mechanism of action	Drugs
Direct atrial electrophysiological effects	
Increase of atrial automaticity	Adenosine, digoxin, doxorubicin, dopamine, marihuana, nicotine, sympathomimetics, sumatriptan, theophylline
Slow intra-atrial conduction	Bisphosphonates, bupivacaine, digoxin, flecainide, gemcitabine, paclitaxel
Shorten atrial APD/ERP	Adenosine, arbutamine, digoxin, dobutamine, dopamine, dopexamine, flosequinan, hexoprenaline, marihuana, milrinone, nicotine, physostigmine, sildenafil, terbutaline, vardenafil, xanthines
Changes in cardiac autonomic tone	
Increase vagal tone	Acetylcholine, adenosine, apomorfine, digoxin, marihuana
Increase sympathetic tone	AAS, adenosine, arbutamine, atropine, dobutamine, dopamine, dopexamine, flosequinan, hexoprenaline, marihuana, milrinone, nicotine, sildenafil, terbutaline, vardenafil
Myocardial ischemia	
Coronary vasoconstriction/thrombosis	Acetylcholine, alemtuzumab, alkylating agents, bevacizumab, antimetabolites, docetaxel, 5-FU, IL-2, marihuana, ondansetron, paclitaxel, sorafenib, sumatriptan, sunitinib
Direct myocardial damage	
Cardiac fibrosis/hypertrophy	AAS, anthracyclines, bisphosphonates, alkylating agents, gemcitabine, nicotine, sunitinib
Heart failure	Antracyclines, alkylating agents, capecitabine, docetaxel, 5-FU, mitomycin, nicotine, paclitaxel, sorafenib, sunitinib, trastuzumab
Abnormalities in calcium homeostasis	Alemtuzumab, anthracyclines, bisphosphonates, dopamine, dobutamine, etanercept, milrinone
Myocarditis, Pericarditis	Alemtuzumab, Alkylating agents, 5-FU, cyclophosphamide, IL-2
Other mechanisms	
Release of proinflammatory cytokines	Alemtuzumab, alkylating agents, anthracyclines, antimetabolites, bisphosphonates, docetaxel, fluorescein, 5-FU, gemcitabine, rituximab, paclitaxel
Increased oxidative stress	Alkylating agents, anthracyclines, antimetabolites, mitomycin
Hypotension*	Apomorphine, diltiazem, docetaxel, 5-FU, interleukin-2, levosimendan, paclitaxel, sildenafil, vardenafil, vasodilators, verapamil
Electrolyte disturbances	Amsacrine, bisphosphonates, cisplatin, glucocorticoids melphalan, thiazides

*Indirect increase in sympathetic tone.
5-FU: 5-fluorouracil; AAS: Androgenic-anabolic steroids; IL-2: Interleukin-2.

artery disease [23-29], but the prevalence is higher in elderly patients [30,31]. Risk predictors of AF include history of AF, atrial dilatation, right bundle branch block, bradycardia, and hypertension [26]. Sinus rhythm recovers spontaneously or following the administration of digoxin or metoprolol. However, one patient presents a permanent AF after dobutamine (**Table 5**) [32].

Short-term milrinone increases the risk of AF or flutter (4.6% vs. 1.5%) in patients with acute decompensated heart failure [33] and in patients undergoing elective cardiac surgery, perioperative enoximone [34] and milrinone [35] increase the risk of postoperative AF. In a comparative study between dobutamine and milrinone in patients after cardiac surgery, AF occurs more often during the dobutamine infusion [36]. Dopamine and dobutamine increase cAMP levels by activating β1-adrenergic receptors, while milrinone decreases cAMP degradation by inhibiting phosphodiesterase III. All these agents shorten AAPD and AERP and increase focal ectopic automaticity attributable to delayed or early afterdepolarizations in the pulmonary veins [37,38]. Additionally, they increase atrioventricular nodal conduction and may increase the ventricular rate in patients with AF.

In a comparative study with dobutamine, levosimendan-treated patients present a higher incidence of AF, possibly because the high dose of levosimendan used in this study produces a more marked and long-lasting hypotensive response [39].

4.2.3 *Antiarrhythmics*

Antiarrhythmics used in the treatment of AF can also produce proarrhythmic adverse effects, including AF [40]. In patients with paroxysmal AF, the estimated treatment success of flecainide is 74%, but DIAF is observed in 1.3% of the patients (**Table 2**) [41]. Flecainide-induced AF can be explained by the potent blockade of Na^+ channels that slows intra-atrial conduction velocity, an effect that is usually more prominent in diseased tissues and at fast heart rates. Amiodarone is the most effective drug for maintaining sinus rhythm, but it can induce AF in patients who develop type I hyperthyroidism during or after termination of amiodarone treatment. Amiodarone-induced DIAF can be reversed with propylthiouracil and propranolol (**Table 5**) [42,43]. Additionally, amiodarone inhibits the peak inward Na^+ current in a frequency- and voltage-dependent manner and

Table 5. Case reports of drug-induced atrial fibrillation.

Drug* [Ref.]	Age (Yrs), Sex, Other diseases	Reversion to SR	Clinical use
Adenosine [54]	5, during EPS	Reversed spontaneously	Conversion to sinus rhythm of paroxysmal SVT
Adenosine [55]	30, during EPS	6.6%, 1 sustained AF	
Adenosine [56]	4, during myocardial perfusion scintigraphy	Reversed spontaneously	
Adenosine [57]	38 children, during EPS	Reversed spontaneously	
Adenosine [58]	26, W	ECV	
Adenosine [59]	160, wide or narrow complex tachyarrhythmias	1 AF. Reversed spontaneously	
Alemtuzumab (Phase II) [111]	76, T-prolymphocytic leucemia	1 AF	Monoclonal antibody to CD52
Alemtuzumab (Phase II) [112]	8, mycosis fungoide/Sézary syndrome	1 AF. Reversion a few days after discontinuation	Chronic lymphocytic leukemia
Amifostine [177]	58, various types of malignancy	5,2%. Reversed spontaneously	Chemotherapy agent
4-Aminopyridine [178]	56, M, accidental overdosed	Electrical cardioversion	Multiple sclerosis
Aminophylline [175]	3, COPD	Reversed spontaneously	Bronchodilator agent (theophylline with ethylenediamine)
Amiodarone-induced thyrotoxicosis [42]	53, M, dilated cardiomyopathy	Propylthiouracil and propranolol	Class III antiarrhythmic drug
Amiodarone-induced thyrotoxicosis [43]	60, M, obstructive HCM		
Anabolic Steroids [156]	36, M, (testosterone ethanate and stanozolol), atrial dilatation	Electrical cardioversion	Anabolic agent
Anabolic Steroids [157	22, M, bodybuilder, atrial hypertophy (testosterone cypionate, extrabolin decanoate and stanozolol)	Reversed spontaneously	
Apomorphine s.c. [142]	65, M, esophageal cancer	Reversed with amiodarone	Parkinson's disease
Arbutamine for stress echocardiography [146]	69, pharmacological stress testing	Reversed spontaneously	Diagnosis of CAD
Atropine, ophthalmic [128]	3, after trabeculectomy for glaucoma	2 ECV, 1 spontaneously recovered	Long acting mydriatic and cycloplegic
Azathioprine [113]	52, M, ulcerative colitis	Reversed with propafenone	Immunosuppressive agent
Azathioprine [114]	60, M, psoriasis, heavy alcohol consumption	AF after rechallenge. Spontaneously recovered	
Azathioprine [115]	53, M, widespread bullae		
Azathioprine [116]	62, F, ulcerative colitis	Reversed with amiodarone	
Bupivacaine [143]	77, M, stable angina pectoris	Reversed with digoxin and propranolol	Local anesthetic
Carboplatin, paclitaxel and gemcitabine (Phase II) [83]	17, NSCLC plus amifostine	1 AF	Antichemotherapy therapy
Cetuximab and cisplatin (Phase II) [73]	22, advanced squamous cell head and neck cancer	4.5%. Electrical CV	Antichemotherapy therapy
Cisplatin [74]	65, M, hypedrtensive, lung carcinoma	Reversed with amiodarone	Chemotherapy agent
Cisplatin and 5-FU [75]	76, advanced cancer	1 AF. Received digoxin	Chemotherapy agent
Cisplatin and etopoxide [76]	65, W	2 episodes of AF. 1 reversed spont aenously, 1 required antiarrhythmic treatment	Chemotherapy agent
Cisplatin plus 7-hydroxy-staurosporine (Phase I) [77]	10, advanced malignant solid tumors	1 AF	Chemotherapy agent
Clenbuterol [173]	31, M, bodybuilder		Bronchodilator agent

*Drugs are listed alphabetically.

COPD: Chronic obstructive pulmonary disease; ECV: Electrical cardioversion; EPS: Electrophysiological study; HCM: Hypertrophic cardiomyopathy; IV: Intravenously; NSCLC: Non-small cell lung cancer; S.C.: Subcutaneous. SR: Sinus rhythm; SVT: Supraventricular tachycardia.

Table 5. Case reports of drug-induced atrial fibrillation (continued).

Drug* [Ref.]	Age (Yrs), Sex, Other diseases	Reversion to SR	Clinical use
Clozapine [131]	69, M, paranoid schizophrenia	Reversed with digoxin after 2 days	Antipsychotic agent
Cyclophosphamide and MESNA [78]	56, M, multiple myeloma	Reversed with IV digoxin	Immunosuppressive agent
Cyclosporine [179]	75, M	Reversed spontaneously	Immunosuppressive agent
Depsipeptide [186]	37, refractory neoplasms	2.7%. No recurrence when retreated	Chemotherapy agent
Dobutamine [32]	73, M, morbid obesity, atrial enlargement	Persistent AF despite ECV	Stress echocardiography
Docetacel [117]	46, W, infiltrating ductal carcinoma	Reversed spontaneously	Chemotherapy agent
Doxorrubicin [118]	74, M, small cell carcinoma of the lung	Reversed with digoxin	Chemotherapy agent
Doxorrubicin [119]	53, M, diffuse large B-cell gastric lymphoma	Inefective ECV. Reversed with amiodarone and verapamil	
Etanercept and methotrexate [181]	57, M, nodular rheumatoid arthritis	New-onset AF after 5 months of therapy	Nodular rheumatoid arthritis
Fluorescein IV [193]	65, M, ankle surgery	ECV	Tracer for angiography
Fluoxetine [129]	Elderly woman, chronic stable angina	AF that recurred on drug rechallenge	Antidepressive agent
Fluticasone [182]	15 asthmatic boy	Reversed spontaneously	Steroidal anti-inflammatory agent
Gemcitabine [100]	65, M, non-small cell lung cancer	Converted with amiodarone	Chemotherapy agent
Gemcitabine [101]	78, M, pancreatic adenocarcinoma, mild mitral valve prolapse, complete right bundle branch block	AF upon rechallenge. Reversed with propafenone	
Gemcitabine [102]	70, M, pancreatic adenocarcinoma	Reversed spontaneously	
Gemcitabine [103]	2, W, NSCLC	Reversed with amiodarone and digoxin	
Hexoprenaline [152]	20, W, 33 weeks of gestation	Reversed spontaneously after 8 h	Tocolytic agent
Ibuprofen [183]	35, M	Converted with amiodarone	Nonsteroidal anti-inflammatory agent
Interleukin-2 [109]	199 (310 courses), metastatic melanoma or renal cell carcinoma	2 AF. Reversed spontaneously	Chemotherapy agent
Interleukin-11 [184]	33, bone marrow failure	Reversed spontaneously	Stimulation of mega karyocyte maturation
Ipratropium [185]	71, W, asthmatic	Reversed spontaneously	Treatment of acute asthma or COPD
Lacosamide [135]	226, diabetic neuropathy	3 AF. Reversed spontaneously	
Lacosamide [136]	37, W, partial seizures	Persistent AF. Resolved with drug discontinuation	Treatment of partial-onset seizures and diabetic neuropathic pain
Marihuana [192]	Review of 7 cases from the literature	No recurrence after cessation of marihuana smoking	Ilicit drug
Melphalan high-dose [79]	27, advanced multiple myeloma	2 AF. Reversed with amiodarone	
Methylprednisolone [14]	72, W, Crohn's disease	Reversed spontaneously	Steroidal anti-inflammatory agent
Methylprednisolone [15]	41, M, membranoproliferative glomerulonephritis	Reversed with metoprolol. No AF with fluocortolone	

*Drugs are listed alphabetically.

COPD: Chronic obstructive pulmonary disease; ECV: Electrical cardioversion; EPS: Electrophysiological study; HCM: Hypertrophic cardiomyopathy; IV: Intravenously; NSCLC: Non-small cell lung cancer; S.C.: Subcutaneous. SR: Sinus rhythm; SVT: Supraventricular tachycardia.

Table 5. Case reports of drug-induced atrial fibrillation (continued).

Drug* [Ref.]	Age (Yrs), Sex, Other diseases	Reversion to SR	Clinical use
Methylprednisolone [16]	37, M, with lupus erythematosus	Reversed spontaneously	
Methylprednisolone [17]	22, M	Reversed spontaneously	
Methylprednisolone [18]	2 children, 1 with systemic lupus erythematosus, 1 with nephritic syndrome	1 reversed with disopyramide, 1 spontaneously	
Metaproterenol [186]	40 asthmatic patients	Reversed spontaneously	Bronchodilator agent
Methotrexate [187]	36, W, osteosarcoma	Reversed spontaneously	Chemotherapy agent, soriasis and rheumatoide arthritis
Mitoxanthrone [120]	73, multiple esclerosis	1 AF (patient with previous IHD)	Antineoplastic agent
Nicotine [189]	35, M, chewing nicotine gum for smoking withdrawal	Reversed with digoxin	Alternative to tobacco
Nicotine gum [190]	39, M	ECV after ibutilide	
Nicotine gum [191]	52, M, coronary artery disease	Reversed with propranolol	Alternative to tobacco
Nifedipine [155]	38, W, preterm labour	ECV	Antihypertensive and antianginal agent
Olanzapine [132]	47, M, bipolar disorder	Reversed sponatenously	Antipsychotic drug
Olanzapine [133]	21, W	Reversed sponatenously	
Ondansetron [139]	47, W, hypertensive	Reversed with procainamide	Treatment and prevention of chemotherapy-induced nausea and vomiting
Ondansetron [140]	51, M, recurrent inguinal hernia	ECV after 16 h	
Paclitaxel [98]	62, W, NSCLC	Reversed with digoxin and propafenone	Chemotherapy agent
Paclitaxel [99]	58, breast cancer	1.7%. Reversed spontaneously	
Paliperidone [134]	46, M, bipolar disorder, DM, hyperlipidemia and hypertension	Reversed with diltiazem	Antipsychotic drug
Physostigmine [145]	55, W, slow recovey from anesthesia	Reversed spontaneously	Reverse central anticholinergic syndrome, myastemia gravis, glaucoma
Pseudoephedrine [147]	2 infants (< 1 y), high-dose (> 4 mg/kg/day)	Reversed spontaneously	Upper resperatory descongestant
Rituximab [104]	131, mantle-cell lymphoma	2 AF.	Chemotherapy agent
Salbutamol [179]	19, F, chronic salbutamol inhalation	Reversed spontaneously	Bronchodilator
Salbutamol [170]	18, COPD and concurrent heart disease	8 SVT or PAF	
Salbutamol [178]	26, M, asthmatic	AF episodes when using a spacer	
Sildenafil [148]	55, M, WPW syndrome	Reversed spontaneously	Erectile dysfunction
Sildenafil [149]	50, M, HCM	Reversed with esmolol	
Sildenafil [150]	Healthy young man	Failed ECV twice. Reversed after 2 days	
Sumatriptan [137]	34, M, with migraine	Reversed spontaneously	Migraine headaches
Sumatriptan [138]	53, M	ECV	
Sunitinib [121]	57, M, metastatic renal cell carcinoma	Reversed with amiodarona	Chemotherapy agent
Terbutaline [153]	30, F, twin gestation at 35 weeks	Reversed with procainamide	Bronchodilator, tocolytic
Terbutaline [154]	20, W, gravid	Reversed with diltiazem	
Theophylline [175]	38 patients with acute poisoning	5.3%	COPD and asthma
Theophylline [176]	12, asthma and spastic bronchitis	Reversed spontaneously	

*Drugs are listed alphabetically.

COPD: Chronic obstructive pulmonary disease; ECV: Electrical cardioversion; EPS: Electrophysiological study; HCM: Hypertrophic cardiomyopathy; IV: Intravenously; NSCLC: Non-small cell lung cancer; S.C.: Subcutaneous. SR: Sinus rhythm; SVT: Supraventricular tachycardia.

Table 5. Case reports of drug-induced atrial fibrillation (continued).

Drug* [Ref.]	Age (Yrs), Sex, Other diseases	Reversion to SR	Clinical use
Thiazides [19]	3 hypertensives with hypokalemia		Hypertension and heart failure
Trastuzumab [122]	69, F, breast cancer	Reversed spontaneously	
Trazodone [130]	78, W, uterine prolapse	Reversed spontaneously after drug discontinuation	Antidepressant agent
Vardenafil [151]	50, M, healthy	Reversed with diltiazem	Erectile dysfunction
Verapamil IV [49]	26, M, healthy	Reversed spontaneously	Antihypertensive, antianginal and antiarrhythmic agent
Verapamil [22]	100, consecutive	Reversed spontaneously	
Yohimbine [188]	38, M, type 1 diabetes	Reversed spontaneously	Erectil impotence

*Drugs are listed alphabetically.
COPD: Chronic obstructive pulmonary disease; ECV: Electrical cardioversion; EPS: Electrophysiological study; HCM: Hypertrophic cardiomyopathy; IV: Intravenously; NSCLC: Non-small cell lung cancer; S.C.: Subcutaneous. SR: Sinus rhythm; SVT: Supraventricular tachycardia.

slows intra-atrial impulse conduction worsening preexisting intra-atrial conduction abnormalities [44]. It can be hypothesized that this effect can also contribute to amiodarone-induced AF [43].

Diltiazem and verapamil are two non-dihydropyridine L-type Ca^{2+} channel blockers widely used to slow heart rate during AF and terminate supraventricular tachycardias. However, verapamil increases atrial vulnerability and duration of electrically-induced AF in patients with paroxysmal AF [45], atrioventricular reentry, and permanent junctional reciprocating tachycardia [46]. Verapamil also precipitates AF in patients with hypertrophic cardiomyopathy [47] and with paroxysmal supraventricular tachycardia (**Table 2**) [48]. Verapamil does not affect AERP, but rapid intravenous administration of verapamil results in hypotension and reflex sympathetic activation [49]. Thus, patients with paroxysmal AF should be carefully evaluated before prescribing diltiazem and verapamil [50].

Approximately 3% of patients receiving adenosine for treating supraventricular tachycardias, and 11 – 16.2% of those receiving adenosine during electrophysiologic studies develop transient AF (**Table 2**) [51,52]. In a retrospective study, AF occurs in 15% of patients with atrioventricular-AV reentry and 17% with permanent junctional reciprocating tachycardia [53]. Moreover, several case reports of adenosine-induced DIAF have been described (**Table 5**) [54-59]. Because of its short half-life, adenosine-induced AF subsides spontaneously within seconds or a few minutes. Adenosine increases in atrial automaticity and shortens AAPD and AERP by activating the acetylcholine-sensitive outward K^+ current ($I_{KAch/Ado}$) [60,61]. Adenosine also produces a reflex increase in circulating catecholamine levels, frequently followed by an abrupt shift toward vagal predominance. The resulting decrease in wavelength facilitates the coexistence of multiple re-entrant atrial wavelets and predisposes to AF in the susceptible atrium [51].

Pulmonary vein isolation is an effective treatment for AF, but many patients require repeated ablations due to resumption of electrical conduction in previously isolated pulmonary veins [62]. Adenosine acutely reconnects pulmonary veins post-ablation, revealing "dormant conduction" between pulmonary veins and the left atrium [63]. In a canine model, radiofrequency–induced pulmonary vein disconnection produces a depolarization of the resting potential to voltages positive to -60 mV that fully inactivate Na^+ channels. Interestingly, the depolarizing effect is less marked in pulmonary veins with dormant conduction [64]. Adenosine hyperpolarizes the membrane potential (~10 mV) by selectively activating the G protein-coupled K^+ current I_{Kado} in pulmonary veins. This affect returns the resting membrane potential in dormant veins to voltages negative to –60 mV, at which excitability is restored [64]. Isoproterenol also produces a hyperpolarizing effect but adenosine-induced changes are greater [65]. These findings provide a new hypothetical mechanism by which a drug that hyperpolarizes the resting membrane potential may facilitate reconnection of previously isolated pulmonary veins and reinduce AF.

At therapeutic doses digoxin, because of its vagotonic properties, produces a nonuniform shortening of AAPD and AERP which may increase the duration and incidence of paroxysmal AF [66]. At supratherapeutic concentrations, digoxin increases ectopic automaticity and slows intracardiac conduction, facilitating the perpetuation of paroxysmal AF.

4.2.4 *Vasodilator drugs*

Flosequinan increases heart rate and facilitates atrioventricular nodal conduction, increasing the ventricular rate in patients with AF [67]. These effects could result from a direct drug action (phosphodiesterase inhibition) or reflex sympathetic activation. This latter mechanism can explain some case reports of AF induced by some vasodilators [3].

4.3 Cancer chemotherapy

Cardiovascular toxicity is a progressively increasing complication of cancer chemotherapy. Indeed, even after exclusion of confounding factors, AF was 3.5 times as likely in patients with first diagnosis of colorectal cancer compared with controls [68]. Several anticancer drugs produce AF (**Tables 3** and **5**). The incidence and

severity of DIAF depend on the drugs used, dose and schedule employed (particularly with combination therapy), age of patients, and presence of an arrhythmogenic substrate created by the cancer and/or chemotherapy. Furthermore, postoperative AF can complicate the outcome in up to 20% of patients with malignancies undergoing cardiothoracic surgery [69,70].

Anthracyclines (doxorubicin, mitoxantrone) produce paroxysmal AF in 1.3 – 10.3% of patients within the first 24 h postinfusion [71,72]. Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan) can also induce AF [73-79]. Intrapericardial and intrapleural infusion of cisplatin in patients with lung adenocarcinoma or pleural mesothelioma and cardiac tamponade induces paroxysmal AF in 12 – 32% of patients [80-82]. In two Phase II trials including combination therapy with carboplatin, AF appeared in 1 patient [83]. High-doses of cyclophosphamide and ifosfamide are associated with supraventricular tachycardia and AF, particularly in patients with decreased kidney function and/or cardiomyopathies [84,85]. High-dose melphalan prior to a bone marrow transplant produces AF in 6.6 – 8.3% of patients [86-88] (1.7 – 22.5% in the elderly) [89,90], while AF does not occur in patients transplanted without melphalan. AF began at variable intervals, but sinus rhythm is restored within 72 h. Patients with AF are older, with higher baseline creatinine, larger left atrial size, and more cardiac comorbidities and present prolonged longer hospitalizations [88].

There are cases of AF appearing 12 – 24 h after gemcitabine infusion, resuming sinus rhythm spontaneously or after antiarrhythmic treatment. It was proposed that 2',2'-difluorodeoxyuridine, an active metabolite with a half-life of approximately 18 – 24 h, could be responsible for AF [91,92]. AF appeared in patients receiving antimetabolite-based [5-fluorouracil (5-FU), capecitabine] chemotherapy combinations [93-95]. Two out of 25 patients receiving 5-FU present an increase in P wave duration and dispersion on the ECG [96], effects that may be predictive of patients at risk of developing DIAF. AF or flutter appears in 8.2% patients with metastatic non–small-cell lung cancer treated with gemcitabine and/or vinorelbine [97] and in 5.8% of those receiving the combination of carboplatin [83], paclitaxel [98,99], and gemcitabine (**Table 5**) [100-103].

In the National Cancer Institute database, there were 8 cases of taxol-induced atrial arrhythmias that start after several hours and reverse after drug discontinuation [91]. Rituximab is associated with infusion reactions, including AF, reversible upon drug discontinuation (**Table 5**) [104]. Between 1.9% and 13.3% of patients with metastatic melanoma or renal cell carcinoma receiving courses of interleukin-2 develop AF or supraventricular tachycardia rapidly reversible to sinus rhythm (**Table 3**) [105-109]. In 317 patients treated with 423 courses of interleukin-2, 8% of the courses are associated with AF and 0.2% with non-sustained supraventricular tachycardia [106]. Finally, in 4,443 patients treated with amsacrine, 29 developed cardiac arrhythmias (0.6%) within minutes to several hours after drug administration, including 3 patients with AF/flutter [110]. Isolated reports DIAF have been described with alemtuzumab [111,112], azathioprine [113-116], docetaxel [117], doxorubicin [118,119], mitoxanthrone [120], sunitinib [121], and trastuzumab (**Table 5**) [122]. A man with severe psoriasis treated with azathioprine develops a paroxysmal AF which resolved within a few hours and reappears after rechallenge [114].

4.3.1 *Mechanisms of chemotherapy-induced AF*

Multiple mechanisms have been proposed to explain how cancer chemotherapy may induce AF including (**Table 4**): i) drug-induced cardiac injury (hypertrophy, fibrosis, diffuse interstitial edema, inflammation) associated with myocarditis, pericarditis, cardiomyopathies, or heart failure, that create an arrhythmogenic substrate for the development/maintenance of AF [70,91,92,123,124]. ii) Myocardial ischemia secondary to vasospasm, arteritis, or coronary artery thrombosis due to activation of the coagulation system. Coronary vasospasm has been related to a direct toxic effect on coronary endothelium, involving the inhibition of endothelial nitric oxide synthase, an endothelium-independent vasoconstriction via protein kinase C or the release of vasoactive compounds. iii) Hypertension, often seen with antiangiogenic agents, or hypotension, leading to reflex sympathetic activation. iv) Generation of reactive oxygen species leading to oxidative stress, cardiomyocyte apoptosis, and progressive reduction in cardiac function. Anthracyclines can also depress cardiac antioxidant defense systems (catalase and glutathione peroxidise activity). v) Alterations in mitochondrial calcium transport. vi) Electrolyte disturbances, particularly hypokalemia. vii) Inflammation plays an important role in carcinogenesis and may represent a link between AF and cancer. Indeed, lymphomononuclear inflammatory infiltrates are found in biopsies from patients with lone AF [125] and C-reactive protein levels, a marker of systemic inflammation, are higher in patients with persistent or paroxysmal AF [126] and with a history of cancer [68,69]. The inflammatory reaction can be mediated by an autoimmune paraneoplasic syndrome leading to the release of proinflammatory cytokines, myofibroblast proliferation, and collagen deposits in the atrium [68,127]. Interestingly, cancer was not found to be an independent predictor of AF in multivariable analysis, suggesting that malignancy does not lead to AF per se, but does so through systemic inflammation.

4.4 Central and peripheral nervous system drugs

4.4.1 *Anticholinergics*

Cardiac arrhythmias are among the major adverse reactions of anticholinergics. Two cases of paroxysmal AF are reported in patients receiving atropine eye drops after trabeculectomy for glaucoma (**Table 5**) [128].

4.4.2 *Antidepressants/antipsychotics*

Isolated cases of DIAF are reported with antidepressants (fluoxetine, trazodone, and tranylcypromine) [3,129,130] and antipsychotics (clozapine, olanzapine, and paliperidone) (**Table 5**) [3,131-134]. In some patients, DIAF requires

antiarrhythmic therapy to restore the sinus rhythm. The potential mechanisms of DIAF were not analyzed, although a direct cardiodepressant effect and an increase in sympathetic tone were suggested. The antiepileptic lacosamide, which enhances the slow inactivation of voltage-gated sodium channels, induces AF in 1.5% of patients with partial-onset seizures, painful diabetic neuropathy, and risk factors for heart disease [135]. In a case report, lacosamide produces a persistent AF in an epileptic patient without cardiovascular risk factors (**Table 5**) [136].

4.4.3 *Serotonergic drugs*

The anti-migraine agent sumatriptan produces paroxysmal AF that reverses spontaneously with positive rechallenge (**Table 5**) [137,138]. Myocardial ischemia secondary to coronary artery vasoconstriction can be the trigger for AF. Two cases of DIAF are reported in patients receiving ondansetron for the treatment of postoperative nausea and vomiting (**Table 5**) [139,140]; both require treatment to recover sinus rhythm. AF might be related to coronary vasospasm, hypotension, inhibition of Bezold–Harish cardiac reflex and/or unopposed action of other serotonin receptors [141].

4.4.4 *Dopamine agonists*

The subcutaneous bolus of apomorphine produces within 5 min an episode of AF that requires antiarrhythmic therapy to recover sinus rhythm (**Table 5**) [142]. DIAF may be related to an increase in vagal tone.

4.4.5 *Local anesthetics*

Bupivacaine induces AF in a man with stable angina pectoris during epidural anesthesia (**Table 1**) [143]. The mechanism of DIAF seems to be related to its potent sodium channel blocking properties. It is unlikely that bupivacaine increases atrial automaticity in partially depolarized atrial cells due to an inhibition of the Na^+-K^+ pump because this effect appears only at supratherapeutic concentrations [78].

4.4.6 *Parasympathomimetic drugs*

Paroxysmal AF is a common complication (17%) following intracoronary injection of acetylcholine for the provocation of coronary spastic angina (**Table 1**) [144]. Spontaneous conversion occurs within 15 min in 71.6% of patients, but 28.4% need antiarrhythmics for the cardioversion of AF to sinus rhythm. Sporadic cases of paroxysmal AF are described with the cholinesterase inhibitors physostigmine (in a patient with a slow recovery from anesthesia) (**Table 5**) [145] and donepezil [3]. The potential mechanism is related to an increase in vagal tone and a shortening in AAPD and AERP, although myocardial ischemia due to a coronary vasospasm may be the trigger for AF.

4.4.7 *Sympathomimentic agents*

Arbutamine, a beta-adrenergic agonist, can induce paroxysmal AF in 1% of patients when used for stress echocardiography [146]. High doses of the nasal decongestant pseudoephedrine produce AF in infants (**Table 5**) [147].

4.5 Genitourinary system

Paroxysmal AF can appear in healthy men 20 – 60 min after taking sildenafil [148-150] or vardenafil (**Table 5**) [151]. AF may be related to reflex sympathetic activation secondary to drug-induced hypotension and shortening of AAPD. DIAF can appear following the administration of β2-adrenoceptor agonists (hexoprenaline, terbutaline) [152-154] and nifedipine [155] for treatment of premature labour. Three women require pharmacological cardioversion to restore the sinus rhythm (**Table 5**). An asymptomatic paroxysmal AF occurring at low serum levels of the drug was reported during intravenous magnesium sulfate treatment of preeclampsia [3].

4.6 Hormones

Two case reports link high-doses of anabolic-androgenic steroids (AAS) in bodybuilders with AF. The arrhythmia spontaneously converts and does not recur after drug discontinuation [156,157]. AAS-induced AF may be related to structural changes (atrial hypertrophy and fibrosis) leading to increased heterogeneity in atrial conduction and changes and cardiac autonomic dysfunction (impairment of parasympathetic control, increased sympathetic activity) [158].

4.7 Metabolic drugs

Two randomized trials suggest that bisphosphonates increase the risk of serious AF (defined as events resulting in hospitalization or disability or judged to be life-threatening) in women with postmenopausal osteoporosis. In the *HORIZON Pivotal Fracture Trial* intravenous zoledronic acid increases the risk of serious AF as compared to placebo (**Table 1**), but not the risk of all AF events [159]. The majority of events occur more than 30 days after infusion, when the drug is not detectable in plasma. Similarly, in the *Fracture Intervention Trial* study, alendronate tends to increase the incidence of serious AF [160]. However, another two studies did not find differences in the incidence of AF in patients treated with zoledronic acid or risedronate [161,162]. Four case-control studies analyze the association between AF and bisphosphonate use. In one study alendronate use increases the risk of AF [163], whereas three studies using databases from Denmark and the United Kingdom do not find that bisphosphonate use increases such a risk [164-166]. In one of these studies, the risk was higher in users of elandronate than in users of the less potent bisphosphonate etidronate, and the authors suggested that the increased occurrence of AF in fracture patients treated with oral bisphosphonates should be attributed to targeting of bisphosphonates to patients who are already at increased risk of cardiovascular events. [165]. Although in this study bisphosphonate-treated patients are at increased risk of hospital-treated AF, there is no evidence of an increased risk of ischemic stroke or myocardial infarction. A post-hoc analysis of the UK General Practice Research Database find an increased risk of AF or flutter during

the first few months of alendronic acid therapy, but no evidence of an overall long-term increased risk of AF with alendronic acid or risedronate [166]. However, because of the heterogeneity of existing evidence and paucity of information on some agents, the risk of AF associated to bisphosphonates requires further investigation.

Bisphosphonates can induce AF by several mechanisms [160,162,167]: i) an acute-phase response characterized by the release of proinflammatory cytokines, that is, C-reactive protein, interleukin-6, and tumor necrosis factor alpha; ii) a decrease in serum calcium and phosphate levels that can produce a secondary hyperparathyroidism that may impact cardiac conduction; and iii) long-term cardiac structural changes, including progressive fibrosis, as bisphosphonates are non-selective inhibitors of matrix metalloproteinases.

4.8 Respiratory system drugs

Drugs used to treat asthma and/or COPD can produce cardiac arrhythmias, including AF (**Table 1**). In patients from the U.K. General Practice Research database oral short-term use of steroids and theophylline increases the risk of AF, especially with new courses of therapy [12]. However, a weak association is observed for short-term use of inhaled steroids, beta-adrenegic agonists and antimuscarinics. In the UK THIN (The Health Information Network) database, long-acting inhaled bronchodilators, tiotropium and long-acting β-agonists (LABA: salmeterol and formoterol) users present a similar risk of AF/flutter (HR 0.60; 95% CI 0.25, 1.42) [168].

4.8.1 *Sympathomimetic drugs*

Salbutamol can produce AF when used as bronchodilator (**Table 5**) [169-171]. A patient develops AF when using salbutamol via a metered-dose inhaler with a spacer device, which reappears after rechallenge and disappears when the device is discontinued [171]. This finding suggests that DIAF results from increased drug deposition when used with a spacer device. Paroxysmal AF and supraventricular tachycardia appear in 10 out of 18 patients with COPD and structural heart disease treated with salbutamol [170]. Addition of oral theophylline has no influence on the severity of AF. However, in 1,429 patients with COPD, inhaled long-acting beta-2 agonists (arformoterol and salbutamol) do not increase the rates of AF/flutter compared with the placebo group. The rates of the other more serious arrhythmias do not increase with LABA treatment and are similar to placebo [172]. A case report describes an episode of AF with clenbuterol [173], a β2-adrenergic agonist, used by body builder because of its anabolic and lipolytic properties (**Table 5**).

4.8.2 *Xanthines*

Intravenous aminophylline induces AF in 3 patients with COPD [174]. AF reverses to sinus rhythm after 9 – 14 h and reappears after aminophylline rechallenge. In patients with asthma and spastic bronchitis IV theophylline increases heart rate and produces a bout of AF, which resolves spontaneously (**Table 5**) [175,176]. Theophylline-induced AF may be related to its positive chronotropic effect, a shortening of AAPD and AERP and dispersion of recovery of atrial excitability.

4.9 Miscellaneous

Many other drugs have been associated sporadically with the occurrence of AF (**Table 5**) [177-188]. Paroxysmal AF has been described in patients who consumed nicotine chewing gum over a prolonged period and in patients who smoked while using nicotine patches [189-191]. In all cases, AF disappears after nicotine discontinuation. Nicotine increases directly atrial vulnerability to AF by shortening AERP and focal activity in the pulmonary vein-left atrial junction by promoting triggered activity or, indirectly, by releasing acetylcholine and noradrenaline from cardiac autonomic nerve terminals.

Marihuana smoking has been associated with several cases of AF in young healthy people (starting within minutes to 3 h and lasting up to 12 h) which converted to sinus rhythm by pharmacological means (**Table 5**) [192]. Marihuana induces a sympathetic activation followed by decrease in parasympathetic tone, shortens and increases the dispersion of AAPD and AERP and decreases coronary microcirculation, effects that can explain the episodes of paroxysmal AF observed shortly after marihuana smoking. Intravenous fluorescein induces AF that requires cardioversion to restore sinus rhythm in a healthy patient possibly via an allergic reactions or nonspecific histamine releasing mechanisms initiated by the drug or its metabolites (**Table 5**) [193].

5. Limitations

This review presents several limitations. Many reports were described by noncardiologists, which explain why sometimes the description of the arrhythmia is imprecise, there are no echocardiographic data to evaluate the existence of heart disease, there is a lack of standardization for electrocardiographic monitoring, the treatment of the arrhythmia is omitted (quite frequent in cancer chemotherapy) and the drugs used to convert AF to sinus rhythm are different from those recommended in the guidelines. Moreover, the clinical history of patients developing DIAF is incomplete, so that is difficult to determine whether AF reflects the baseline state of the patient or is a truly adverse effect. Furthermore, some patients are treated with several drugs, so that it is difficult to correctly determine which drug causes DIAF. This is a problem in patients with cancer receiving several chemotherapeutic agents simultaneously and in elderly patients with structural heart disease. How to determine which drug is responsible for AF in patients with malignant glioma treated with "eight-drugs-in-one-day" chemotherapy? [194]. Finally, we have omitted data on caffeine and alcohol, as well as on herbal medicines.

6. Conclusions

Despite the observation that many cardiovascular and noncardiovascular drugs can induce AF, DIAF usually is not taken

into consideration. The incidence of DIAF is unknown and there is no clear evidence on whether it can increase the risk of tromboembolism or mortality. However, DIAF can be clinically relevant, particularly in polymedicated elderly patients who present a high incidence of AF and in patients treated with certain cardiovascular (i.e., adenosine, positive inotropic effects) or noncardiovascular drugs (cancer chemotherapy) and in those with cardiovascular (hypertension, coronary artery disease, heart failure) and pulmonary conditions (COPD, asthma) frequently associated with AF. Further research is needed to gain more insight on DIAF, to determine whether the episode of AF is related to the administration of a given drug and the risk factors for.

7. Expert opinion

AF is the most common sustained cardiac arrhythmia in clinical practice. Although AF is not an immediately life-threatening arrhythmia, it impairs quality of life and increases the risk throughout the cardiovascular continuum, as it is associated with a nearly doubled risk of death and an almost five-fold increase in the risk of stroke. AF increases with age and is associated with a variety of cardiovascular (hypertension, heart failure, and coronary artery disease) and noncardiovascular conditions (diabetes mellitus, COPD, and chronic renal disease). In recent years, it has been reported that a progressively increasing number of drugs widely used in clinical practice, with very different mechanisms of action and clinical applications, can induce AF in patients with or apparently without heart disease. However, the physician/patient is not knowledgeable about this drug side effect.

DIAF can be considered a rare complication, but also an increasing problem, as many drugs commonly used in the diagnosis (i.e., adenosine, dobutamine) and/or treatment of cardiovascular and noncardiovascular diseases (chemotherapy agents) can present this adverse effect. DIAF might be the result of multiple mechanisms, including a direct effect on atrial electrophysiological properties (increasing atrial ectopic activity, slowing atrial conduction velocity and/or shortening atrial potential duration and refractoriness), direct myocardial damage (including hypertrophy, fibrosis, heart failure, abnormalities in Ca^{2+} handling, myocarditis, pericarditis), changes in cardiac autonomic tone, electrolyte disturbances, cardiac ischemia (due to coronary vasoconstriction or thrombosis), release of proinflammatory cytokines, increased oxidative stress, or electrolyte disturbances. However, the mechanisms by which many drugs may induce AF require further investigation.

We found that while the overall incidence of DIAF is unknown, but with a few exceptions, it is likely to be very low (tables 1, 2, 3, and 5), though it can be higher than what has been previously reported. Unfortunately, the real incidence of DIAF is unknown for several reasons, including the following. (i) In most cases DIAF is paroxysmal, spontaneously terminating in a few minutes or hours, even when sometimes the arrhythmia persists for several hours and it is necessary to perform an electrical or pharmacological cardioversion to restore sinus rhythm and to avoid the progression to persistent AF. Due to paroxysmal AF, DIAF is most likely to be underdiagnosed. Since in most cases DIAF is paroxysmal, spontaneously terminates in a few minutes or hours, even when sometimes arrhythmia persists for several hours and it is necessary to perform an electrical or pharmacological cardioversion to restore sinus rhythm and to avoid the progression to persistent AF. The problem of early recognition of AF is greatly aggravated by the often "silent" nature of the arrhythmia [1,2]. In fact, in up to one-third of patients with AF, the patient is not aware of the so-called "asymptomatic AF." (ii) Data on DIAF are scattered in the literature, in papers analyzing outcomes and safety of drugs, but these sources are written in many cases by noncardiologists and thus, they usually did not attract the attention of a cardiology readership. (iii) As a consequence, quite frequently, DIAF produced by noncardiovascular drugs are not analyzed by cardiologists, so that the arrhythmia can be misdiagnosed and the treatment of DIAF is delayed. This explains why sometimes the unclear term of supraventricular arrhythmias is used and in some reports there is no clear distinction between AF and flutter. (iv) The real incidence of DIAF has not been studied in a controlled fashion, as a result of which, in many cases the relationship between drug administration and the incidence of DIAF has not been established. Even in controlled trials the prevalence of PAF could be underestimated, as most studies depend on symptomatic episodes, but asymptomatic PAF is common on Holter monitoring. (v) With some drugs, like chemotherapy agents, the cancer itself creates an arrhythmogenic milieu, so that is difficult to determine whether AF reflects the disease of the patient or is an adverse effect of the treatment. A similar problem is present with adenosine or dobutamine when used in patients with coronary artery disease. Another difficulty is that many patients, particularly elderly patients with several comorbidities are treated, as a rule, with multiple agents, making it difficult to determine which one caused AF.

The onset of DIAF is quite variable, depending on the inducing drug, ranging from a few seconds/minutes after IV administration of adenosine, as expected from its short half-life [51], to several days with some chemotherapy agents or months for amiodarone-induced AF associated to thyrotoxicosis. Sometimes DIAF appears not during the first, but after repeated exposure to the drug. The duration of DIAF is also variable, from a few seconds (adenosine) to hours (albuterol, marihuana), so that in some patients an electrical and/or pharmacological cardioversion is required to restore the sinus rhythm. Risk factors for DIAF are quite variable and are not well characterized. Indeed, DIAF appears in patients with no previous history of AF and without structural heart disease. Although DIAF is frequently preceded by premature atrial contractions and atrial arrhythmias [51] and is expected to occur more frequently in patients with structural heart disease or in those who undergo cardiothoracic surgery, further studies are needed to identify risk factors for DIAF.

An important point is to determine whether the episode of AF is related to the administration of a given drug. In this review, we focus our attention on reports where there is a clear link between the offending drug and AF. The correlation is easy to demonstrate in healthy individuals when AF appears shortly after drug administration (i.e., adenosine, dobutamine, or marihuana) and there is a close temporal relationship between drug pharmacokinetics and initiation/termination of AF. Also when patients are treated with widely used cardiovascular, respiratory, and central nervous system drugs that modify atrial electrophysiological and structural properties or cardiac autonomic tone as they can act as triggers for AF, particularly in patients with previous cardiovascular diseases. Sometimes it is possible to reproduce AF after drug rechallenge. However, rechallenge is only ethical when it concerns a drug that is essential for the treatment of the patient and when a causal role of the drug is still inconclusive [3]. However, causality is more difficult to establish when AF appeared after repeated treatment or several days and weeks after initiation of therapy or when the clinical history does not allow to establish a correlation between drug intake and DIAF. Nevertheless, even when there is a close temporal relationship between drug intake and DIAF, the arrhythmia can be a chance finding resulting from the underlying structural heart disease and/or other treatments undergone by the patient.

If after exclusion of potential confounders a DIAF is suspected/confirmed, discontinuation of the causative agent is recommended. This is enough for spontaneous recovery of sinus rhythm in many patients. If the offending drug is necessary for the patient, it may be advised to restart the drug at a lower dose and monitor the patient adequately for recurrence of AF [3]. If AF recurs, continuous treatment to control AF is needed following the current guidelines for the management of AF [1,2]. Treatment of DIAF is not different from that recommended for paroxysmal AF and involves primarily a rate- or rhythm-control strategy. Depending on the patient's course, the strategy initially chosen may prove unsuccessful and the alternate strategy is then adopted [1,2]. When rate control cannot be achieved or in patients highly symptomatic, direct-current or pharmacological cardioversion can be performed to restore sinus rhythm within the first 24 – 48 hours. However, the effectiveness of rhythm- and rate-control therapies on DIAF has not been adequately studied, as DIAF very rarely lasts for more than 48 hours. Furthermore, randomized trials on rhythm over rate control, upon which guidelines are based, predominantly excluded patients with cancer, renal, and pulmonary diseases. Interestingly, in some patients, AF can be avoided by replacing the causative drug for another compound of the same family (i.e., methylprednisolone by fluocortolone, alendronate or zoledronic acid by risedronate) [15,197].

The scarcity of clinical reports of DIAF despite the widespread use of some of the agents in otherwise healthy patients, together with the identification of mutations in genes encoding Na^+ (SCN5A), Ca^{2+} (CACNA1C), and K^+ channels (KCNQ1, KCNE1, KCNK2, KCNH2, KCNA5, KCNJ2), raises the possibility that DIAF might represent a forme fruste of familial AF. Thus, it is possible that patients presenting DIAF may present a predisposing genetic substrate. Unfortunately, and in contrast to drug-induced torsades de pointes, to our knowledge there is no information on asymptomatic patients who carry silent mutations on AF genes that are insufficient to produce a clinical AF, but that can facilitate the appearance of DIAF. This is not a surprise if we take into consideration that DIAF is ignored or underestimated by both cardiac and noncardiac professionals. Another possible explanation for DIAF is that some mutations may encode cardiac ion channels that are not dysfunctional by themselves, but interact with particular drugs in a manner different from drug interactions with wild-type channels. If so, multiple forms of DIAF can possibly exist depending on the mutated channel and the specific drug involved.

As a consequence of the scarcity of data, it is clear that this review raises more questions than answers. DIAF is a rare complication and physicians are not knowledgeable about this drug side effect and general treatment guidelines for the treatment of AF do not devote much interest in DIAF. Furthermore, the mechanisms of proarrhythmia and the clinical consequences of DIAF are presently unknown and merit further investigation. Because drug-induced paroxysmal AF is an uncommon and transient adverse effect one may think that DIAF might appear to be a benign condition. However, and even when there is some evidence that DIAF can prolong hospitalization [88,165], there is no information on whether it can result in hospitalization, prolong the length of stay in-hospital, or increase the risk of tromboembolic events (i.e., stroke) or mortality. Nevertheless, because paroxysmal AF carries the same risk of stroke as persistent or permanent AF [2,195] and undiagnosed "silent AF" is a likely cause of some cryptogenic strokes [2,196], it is of great interest to understand the significance of DIAF in daily practice and to educate the patients and make them aware of this side effect when some widely used drugs are prescribed. Therefore, there is a lot of work to be done in an attempt to understand the mechanisms of DIAF with different classes of drugs, to identify the risk factors, and to define the incidence and risks of DIAF. Meanwhile, it is necessary that physicians recognize the importance of DIAF in daily practice. DIAF should be suspected in patients with no known risk factors (hyperthyroidism, thoracic surgery) or comorbidities associated with AF (i.e., hypertension, heart failure, coronary artery disease, valvular disease). Finally, patients treated with drugs that induce AF should be instructed to consult with their physicians if their pulse is rapid and irregular or if symptoms associated with DAIF (palpitations, dizziness, shortness of breath, light-headedness, or chest pain) appeared.

Declaration of interest

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