REVIEW ARTICLE

Drug Saf 2011; 34 (6): 465-488
0114-5916/11/0006-0465/$49.95/0

Quinolones
Review of Psychiatric and Neurological Adverse Reactions

Ana M. Tomé and *Augusto Filipe*

Medical Department, Grupo Tecnimede, Sintra, Portugal

Contents

Abstract

Quinolones are a class of antibacterial agents for the treatment of several infectious diseases (e.g. urinary and respiratory tract infections). They are used worldwide due to their broad spectrum of activity, high bioavailability and good safety profile. The safety profile varies from quinolone to quinolone.

The aim of this article was to review the neurological and psychiatric adverse drug reaction (ADR) profile of quinolones, using a literature search strategy designed to identify case reports and case series. A literature search using PubMed/MEDLINE (from inception to 31 October 2010) was performed to identify case reports and case series related to quinolone-associated neurological and psychiatric ADRs. The search was conducted in two phases: the first phase was the literature search and in the second phase relevant articles were identified through review of the references of the selected articles. Relevant articles were defined as articles referring to adverse events/reactions associated with the use of any quinolone. Abstracts referring to animal studies, clinical trials and observational studies were excluded. Identified case reports were analysed by age group, sex, active substances, dosage, concomitant medication, ambulatory or hospital-based event and seriousness, after Medical Dictionary for Regulatory Activities (MedDRA®) coding.

From a total of 828 articles, 83 were identified as referring to nervous system and/or psychiatric disorders induced by quinolones. 145 individual

case reports were extracted from the 83 articles. 40.7% of the individual case reports belonged to psychiatric disorders only, whereas 46.9% related to neurological disorders only. Eight (5.5%) individual case reports presented both neurological and psychiatric ADRs. Ciprofloxacin, ofloxacin and pefloxacin were the quinolones with more neurological and psychiatric ADRs reported in the literature. Ciprofloxacin has been extensively used worldwide, which may explain the higher number of reports, while for ofloxacin and pefloxacin, the number of reports may be over-representative. A total of 232 ADRs were identified from the selected articles, with 206 of these related to psychiatric and/or neurological ADRs. The other 26 were related to other body systems but were reported together with the reactions of interest. Mania, insomnia, acute psychosis and delirium were the most frequently reported psychiatric adverse events; grand mal convulsion, confusional state, convulsions and myoclonus were the most frequently reported neurological adverse events.

Several aspects should be taken into account in the development of CNS adverse effects, such as the pharmacokinetics of quinolones, chemical structure and quinolone uptake in the brain. These events may affect not only susceptible patients but also 'healthy' patients.

1. Introduction

Quinolones are a class of antibacterial agents used for the treatment of several infectious diseases (e.g. urinary and respiratory tract infections). These drugs are used worldwide due to their broad spectrum of activity, high bioavailability and good safety profile.[1]

Quinolones act by inhibiting type II topoisomerases DNA gyrase and topoisomerase IV. These enzymes are involved in bacterial DNA synthesis, being essential for bacterial DNA replication, thereby enabling these agents to be specific and bactericidal. Although some degree of overlap may exist, DNA gyrase tends to be the primary target for quinolones in Gram-negative organisms, whereas topoisomerase IV is typically the primary target in Gram-positive bacteria.[2,3]

Nalidixic acid, a non-fluorinated drug, was the first quinolone to be approved (in 1963, in the US). Since then, structural modifications to the quinolone nucleus and the side-chains produced the first fluoroquinolones (norfloxacin and ciprofloxacin), which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7-position. Subsequent generations of fluoroquinolones were developed to improve the antimicrobial coverage of the previous synthesized fluoroquinolones – high activity against Gram-negative species and atypical pathogens, and good-to-moderate activity against Gram-positive species.[1,4-6] Despite their broad spectrum and clinical success, some fluoroquinolones were withdrawn from worldwide markets because of serious adverse drug reactions (ADRs), i.e. temafloxacin (serious idiosyncratic reactions, such as haemolytic and aplastic anaemia), trovafloxacin (hepatotoxicity), grepafloxacin (QTc interval prolongation) and clinafloxacin (phototoxicity). Gatifloxacin was recently removed from clinical use because of the high incidence of hypo- and hyperglycaemia.[5-9] Some fluoroquinolones are unavailable in the US or other markets, or are used with restrictions (e.g. moxifloxacin,[10] norfloxacin[11]). None of the fluoroquinolones were withdrawn from the market because of neurotoxicity or psychiatric adverse events. Ciprofloxacin and levofloxacin are currently marketed without restrictions and thus are the most widely used fluoroquinolones.

The structure of quinolones may influence the safety profile of this drug class. Position 7 influences binding activity to GABA in the brain, while positions 1 and 7 influence the drug's potency,

pharmacokinetics and potential for interaction with theophylline,[1] which may account for differences in CNS adverse events among quinolones. The risk of seizures and other CNS adverse events may be increased by an increased CNS penetration and either an unsubstituted piperazine (e.g. ciprofloxacin, enoxacin and norfloxacin) or pyrrolidine (e.g. tosufloxacin and clinafloxacin) group at position 7.[1,12]

1.1 Pharmacokinetics

Quinolones are well absorbed following oral administration, with moderate to excellent bioavailability (marginally affected by food), moderate to long elimination half-lives (1.5–16 hours) and volumes of distribution >1.5 L/kg. There are differences in elimination patterns among quinolones, ranging from predominant renal excretion (e.g. ofloxacin, levofloxacin, lomefloxacin, gatifloxacin) to extensive hepatic metabolism (e.g. nalidixic acid, pefloxacin, sparfloxacin and grepafloxacin). Quinolones are also widely distributed throughout the body, with tissue penetration being usually higher than the concentration achieved in plasma, stool, bile, and prostatic and lung tissues, which is not related to lipid solubility. Contrary to this, penetration into prostatic fluid, saliva, bone and CSF does not exceed serum drug levels. These drugs have a relatively poor cerebrospinal fluid (CSF) penetration into uninflamed meninges (table I), but in the presence of an inflammation there is a moderate penetration of at least ciprofloxacin, pefloxacin, ofloxacin and trovafloxacin.[42,43]

Table I. Comparative adverse reaction profile of quinolones and their pharmacokinetic (PK) properties regarding brain tissue penetration

Quinolones	Percentage of adverse reactions by SOC					PK characteristics	References
	GI tract	CNS	skin	hepatic	musculoskeletal		
Ciprofloxacin	++/+++	+	0/+	+	0/+	Distribution in the CSF in concentrations about 10% of those in plasma when meninges are not inflamed	13-15
Gatifloxacin	++/++++	+/+++	0	NA	NA	Distributes into the CNS (mean penetration 35%); CSF: serum concentration ratio of 0.6 (range 0.21–0.45) during multiple-dose administration (400 mg/day)	13-17
Grepafloxacin	++++	+++	++	NA	NA	No data available	15
Levofloxacin	+/++++	+	0/+	+	0/+	Poor penetration into the CNS	13-16,18-38
Moxifloxacin (oral)	+/++++	+/++++	++	NA	NA	No data available in humans; Good penetration into CSF in rabbits was achieved	13,15,39
Norfloxacin	++	+	+	+	+	Widely distributed in body fluids (limited information)	13,15
Ofloxacin	++	++	0/+	+	0/+	Distribution in the CSF but concentrations are higher when meninges are inflamed	13,15
Sparfloxacin	++/++++	++/+++	+/++++	++	0/+	Widely distributed into body tissues and fluids (limited information on CNS)	13-15
Lomefloxacin	NA	NA	NA	NA	NA	Widely distributed into body systems (such as lungs and prostate)	14
Enoxacin	NA	NA	NA	NA	NA	Widely distributed in the body, and concentrations higher than those in plasma have been reported in lungs, kidney and prostate	14
Pefloxacin	NA	NA	NA	NA	NA	Greatest lipophilic character and thus the greatest CNS penetration	40,41
Alatrofloxacin	NA	NA	NA	NA	NA	Prodrug of trovafloxacin, which is widely distributed into body tissues	14

CSF = cerebrospinal fluid; **GI** = gastrointestinal; **NA** = not available; **SOC** = System Organ Class; 0 indicates none or ≤1%, + indicates 1–2%, ++ indicates 2–3%, +++ indicates 3–5%, ++++ indicates >5%.

The penetration of quinolones across the blood-brain barrier (BBB) may be an important factor in determining the relative frequency and severity of CNS toxicity. In general, quinolones have a low lipophilicity, but some can easily cross the BBB.[13,40] Also, they differ considerably in their CSF transport and disposition. For example, pefloxacin has the greatest lipophilic character and thus the greatest CNS penetration;[40,41] therefore, the convulsant activity may be related to pefloxacin concentration in the brain and/or its slow clearance from the cerebral area.[40] On the other hand, ofloxacin and lomefloxacin cross the BBB by a unidirectional efflux (sequestration) process from the CSF into blood by saturable active transport, similarly to that described for some β-lactam antibiotics. It seems that there is the involvement of the efflux transporter P-glycoprotein (which transfers drugs from the brain to the bloodstream, decreasing the apparent distribution of several drugs in brain tissues) or efflux systems, which transport anionic compounds (e.g. multidrug resistance-associated protein 1). The presence of multiple efflux transporters in the brain may also be responsible for the low accumulation of quinolones in this tissue.[40,44]

1.2 Adverse Drug Reaction Profile

The safety profile of this drug class differs from quinolone to quinolone. Their most common adverse events are gastrointestinal disturbances (nausea, vomiting, diarrhoea and abdominal pain). Less common events include neurotoxicity, blood disorders, renal disorders, metabolic disturbances, QTc interval prolongation, hypersensitivity (with anaphylactic shock and anaphylactoid reactions) and photosensitivity reactions.[6,12,45] Phototoxicity is mainly associated with lomefloxacin and sparfloxacin, when patients taking these drugs are exposed to sunlight.[12] Putting ADRs into perspective, gastrointestinal disturbances occur in 2–20% of patients, while CNS events occur in 1–2%, dermatological effects in 0.5–3%, hepatic abnormalities in 2–3% and musculoskeletal disorders <1%.[13] The comparative ADR profile of select fluoroquinolones (for which information on the ADR profile and pharmacokinetics was available) is presented in table I.

Neurological ADRs represent the second most common group of ADRs of this drug class.[13,40] The most commonly reported neurological symptoms are dizziness, headache, insomnia and somnolence. Other less common neuropsychiatric events include delirium, agitation, confusion, psychosis and seizures/convulsions.[1,6,12,13] CNS disturbances can be divided into those resulting from direct effects and those resulting from drug-drug interactions (see section 4).[13]

This review aims to contribute to the characterization of neurological and psychiatric ADR profiles of quinolones using a literature search strategy designed to identify case reports (defined as 'a detailed report of the symptoms, signs, diagnosis, treatment and follow-up of an individual patient', containing, in general, unusual or novel occurrences)[46] and case series ('series of case reports that provide evidence of an association between a drug and an adverse event', being 'generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome').[47]

2. Literature Search Strategy

A literature search was performed based on PubMed/MEDLINE (from inception to 31 October 2010) using the following search terms: 'quinolones', 'fluoroquinolones', 'cinoxacin', 'nalidixic acid', 'oxolinic acid', 'piromidic acid', 'pipemidic acid', 'ciprofloxacin', 'enoxacin', 'lomefloxacin', 'nadifloxacin', 'norfloxacin', 'ofloxacin', 'pefloxacin', 'rufloxacin', 'balofloxacin', 'gatifloxacin', 'levofloxacin', 'moxifloxacin', 'pazufloxacin', 'sparfloxacin', 'temafloxacin', 'tosufloxacin', 'garenoxacin', 'gemifloxacin', 'clinafloxacin', 'prulifloxacin', 'sitafloxacin'; no limits were placed on the search function.

From the results obtained from the literature search, two reviewers selected relevant English, French, Spanish and Portuguese articles related to quinolones by examining the abstracts (selection phase I) independently from each other. Relevant articles were those referring to adverse events or ADRs associated with the use of any

quinolone, regardless of its role (suspected, concomitant or interacting). Abstracts referring to animal studies, clinical trials and observational studies were excluded. Clinical trials and observational studies, regardless of the safety aspect they may cover, were excluded as the main purpose of this review was to evaluate case reports and case series from the literature. The selection of the articles made by each reviewer was compared to determine the abstracts to be included. In the case of doubt or disagreement in the selection of articles, the reviewers included those articles in phase I of the selection process.

Full texts of the selected articles were obtained and the references of those articles reviewed to identify additional case reports and case series (selection phase II). The second phase was conducted using only the references, not the abstracts. The criteria for this phase were the same as mentioned above, as well as the method for the inclusion or exclusion of the articles. Once the selection of the articles was completed and all full text of the selected articles (phase I plus phase II) obtained, a new review of the selected articles was performed to narrow the selection to case reports and case series describing neurological and/or psychiatric adverse event(s)/reaction(s). The selected events belonged to the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) 'Nervous system disorders' and/or 'Psychiatric disorders'. MedDRA® is the international medical terminology developed under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The methodology used in the literature search is detailed in figure 1.

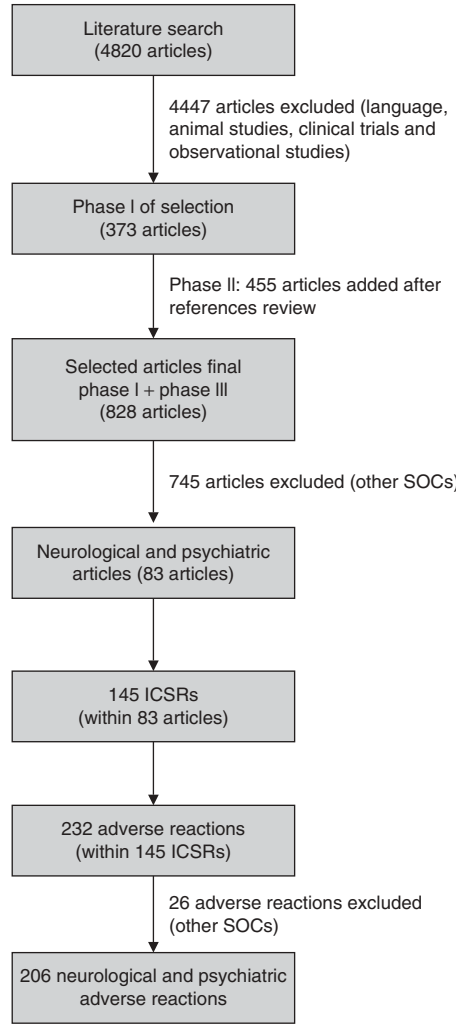

Fig. 1. Flow chart of methodology used in the literature search. **ICSRs** = individual case safety reports; **SOCs** = System Organ Classes.

From the full text of the selected articles, after narrowing the results to neurological and psychiatric adverse event(s)/reaction(s), data were collected using an in-house developed Microsoft Access® database. Each individual case report was recorded using the following criteria, which were according to the guidelines/recommendations by Kelly et al.:[48] ADR verbatim and its description (including information on dechallenge and rechallenge); patients' demographics (sex, age/age group, weight); suspected medicinal product (dosage, pharmaceutical form/route of administration and indication of use); treatment duration; outcome of the reaction; seriousness; causality assessment (when assessed by the authors of the articles); concomitant medication and diseases; past medical and past drug histories, including previous exposure to other quinolones; and place where the event occurred (ambulatory or hospital-based event). The individual case reports were

analysed by age group, sex, active substances, dosage, concomitant medication, ambulatory or hospital-based event and seriousness. Age group was stratified by the following age intervals: ≤18, 19–25, 26–35, 36–45, 46–55, 56–64, 65–74 and ≥75 years. Patients ≤18 years of age were classified as children and adolescents, those aged 19–64 years as adults and those ≥65 years as elderly.

ADRs were coded in MedDRA® version 13.1, using the appropriate Preferred Term. For MedDRA® coding, both reviewers coded each event/reaction individually, and then compared the coding results. In case of disagreement in the MedDRA® coding, the terms coded by the medical expert were the terms selected.

3. Search Findings

From a total of 4820 articles, only 373 were selected as relevant in the first analysis of the articles (phase I). In the second phase, a total of 455 additional articles were selected from the references resulting in a total of 828. From these, 83 (10.0%) articles (case reports and case series) describing neurological and psychiatric ADRs related to one or more quinolones were identified. 145 individual case reports within the 83 articles were analysed, being distributed per SOC, according to the reported ADRs. From the 145 individual case reports, 8 (5.5%) presented both neurological and psychiatric ADRs (belonging to both SOCs), whereas 10 (6.9%) presented neurological and/or psychiatric ADRs combined with ADRs from other SOCs (e.g. 'Investigations', 'Cardiac disorders', 'Gastrointestinal disorders'). A total of 59 (40.7%) of 145 individual case reports belonged exclusively to 'Psychiatric disorders', whereas 68 (46.9%) of 145 belonged to 'Nervous system disorders' only. Identified ADRs are detailed in section 3.4.

3.1 Suspected Drugs

The number of individual case reports of each suspected quinolone and the relevant percentage are detailed in table II. Quinolones included ciprofloxacin, ofloxacin, pefloxacin, norfloxacin, nalidixic acid, levofloxacin, gatifloxacin, cinoxacin, enoxacin, alatrofloxacin, oxolinic acid, piromidic acid, pipemidic acid, lomefloxacin, nadifloxacin, rufloxacin, balofloxacin, moxifloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, garenoxacin, gemifloxacin, clinafloxacin, prulifloxacin and sitafloxacin.

Despite some quinolones no longer being marketed (e.g. gatifloxacin, alatrofloxacin, cinoxacin), the ADRs identified in this literature review were discussed, together with the marketed quinolones.

In general, quinolones were used according to their labelled indications, such as the treatment of respiratory tract infections, urinary tract infections, skin infections and septicaemia. Also, in the majority of the case reports, treatment duration followed the recommendations for treatment durations according to the disease being treated.

3.2 Sex and Age

Data on sex and age were available in 140 individual case reports (96.6%), showing a slightly higher number of ADR reports in women than in men (56.6% vs 40.0%); this difference was not statistically significant. More ADRs were identified in adults (57.2%) than elderly (31.7%) or children/adolescents (6.2%). Among adults and elderly population, there were no major differences in the stratified age groups.

3.3 Dose

Information on dose was available in 122 individual case reports (84.1%) and 104 (71.7%) contained information on the route of administration/pharmaceutical form. The route of administration was mainly *per os* (78 cases [53.8%]). Only two cases reported the administration of topical ciprofloxacin (eye- and eardrops).[49,50]

Patients were treated according to the recommended dose, except in seven cases of overdose or excessive dosage with nalidixic acid[18,51] and ofloxacin[19,20] (two individual case reports each), and ciprofloxacin[21,52,53] (three individual case reports each). The individual case reports of overdose and excessive dosage with nalidixic acid occurred in children. The first case was related to a 14-year-old girl who ingested 6.5 g,[51] where the rec-

Table II. Number and percentages of individual case reports and neurological and psychiatric adverse reactions per quinolone

Quinolone	No. of individual case reports [n (%)]	No. of adverse reactions [n (%)][a]
Ciprofloxacin	72 (49.7)	108 (52.4)
Ofloxacin[b]	34 (23.4)	57 (27.7)
Pefloxacin[b]	14 (9.7)	11 (5.3)
Levofloxacin	8 (5.5)	10 (4.9)
Norfloxacin[b]	6 (4.1)	8 (3.9)
Nalidixic acid	4 (2.8)	4 (1.9)
Gatifloxacin[b]	3 (2.1)	4 (1.9)
Gemifloxacin[b]	2 (1.4)	2 (1.0)
Alatrofloxacin[b]	1 (0.7)	1 (0.5)
Enoxacin[b]	1 (0.7)	1 (0.5)
Balofloxacin[b]	0 (0)	0 (0)
Cinoxacin[b]	0 (0)	0 (0)
Clinafloxacin[b]	0 (0)	0 (0)
Garenoxacin[b]	0 (0)	0 (0)
Lomefloxacin[b]	0 (0)	0 (0)
Moxifloxacin[b]	0 (0)	0 (0)
Nadifloxacin[b]	0 (0)	0 (0)
Oxolinic acid[b]	0 (0)	0 (0)
Pazufloxacin[b]	0 (0)	0 (0)
Pipemidic acid[b]	0 (0)	0 (0)
Piromidic acid[b]	0 (0)	0 (0)
Prulifloxacin[b]	0 (0)	0 (0)
Rufloxacin[b]	0 (0)	0 (0)
Sitafloxacin[b]	0 (0)	0 (0)
Sparfloxacin[b]	0 (0)	0 (0)
Temafloxacin[b]	0 (0)	0 (0)
Tosufloxacin[b]	0 (0)	0 (0)
Total (n)	**145**	**206**

a Percentage of neurological and psychiatric ADRs was calculated excluding the ADRs that did not belong to 'Nervous system disorders' and/or 'Psychiatric disorders'.

b The quinolones that were withdrawn from the market are unavailable in certain countries or are used with restrictions.

ADRs = adverse drug reactions.

ommended daily dose of nalidixic acid in children is 1–2 g. The second case involved a 4-year-old girl who took 800 mg by mistake (excessive dosage).[18] Two cases of overdose after the administration of ofloxacin were also reported: one involved a 14-year-old girl who ingested an unknown amount of ofloxacin and developed an anticholinergic syndrome (concomitant administration of diphenhydramine and chlormezanone);[19] the other occurred in an 81-year-old woman with renal insufficiency who took pefloxacin by mistake after administration of ofloxacin.[20] Two individual case reports of excessive dosage were identified for ciprofloxacin, leading to neurotoxicity. This drug, in a higher than recommended dose for patients with renal impairment, was administered to patients under a chronic dialysis programme[21] and with chronic renal failure.[52] The third case resulted in ballismus, confusional state and irritability in a liver cirrhotic patient,[53] which has a reduced capacity of drug metabolism.

3.4 Adverse Reactions

From a total of 145 individual case reports, 232 ADRs were identified, as some individual

case reports had more than one ADR. From the 232 ADRs, only 206 belonged to the selected SOCs ('Nervous system disorders' and 'Psychiatric disorders'). One of the ADRs, 'EEG abnormal', was included as belonging to one of the above-mentioned SOCs, due to its importance as a tool to identify non-convulsive status epilepticus (see section 4 for further details). The other 26 (11.2%) non-neurological and non-psychiatric ADRs (e.g. palatal disorder, asthenia, fatigue, visual field tests abnormal, liver function tests abnormal, gastrointestinal disorders and cardiac disturbances) were reported, together with the neurological and psychiatric ADRs. For purposes of evaluation, the number of ADRs is considered to be 206 as we are evaluating the profile of neurological and psychiatric ADRs of quinolones.

A total of 111 ADRs (53.9%) belonged to the SOC 'Psychiatric disorders', whereas 95 (46.1%) belonged to the SOC 'Nervous system disorders'. Mania (38 cases; ciprofloxacin, ofloxacin and norfloxacin), insomnia (10 cases; ciprofloxacin and ofloxacin), acute psychosis (8 cases; all ciprofloxacin) and delirium (8 cases; ciprofloxacin, pefloxacin and levofloxacin) were the most commonly reported psychiatric adverse events. Grand mal convulsion (23 cases; all quinolones, except alatrofloxacin and gemifloxacin), confusional state (9 cases; ciprofloxacin, ofloxacin and pefloxacin), convulsions (8 cases; ciprofloxacin, ofloxacin, pefloxacin and gatifloxacin) and myoclonus (6 cases; ciprofloxacin, ofloxacin, pefloxacin and gatifloxacin) were the most commonly reported neurological events. Table III details the neurological and psychiatric ADRs that were reported for each quinolone.

We observed a total of 108 ADRs related to ciprofloxacin, with psychiatric ADRs being the most common (e.g. mania and acute psychosis). Ciprofloxacin was followed by ofloxacin, pefloxacin, levofloxacin, norfloxacin, nalidixic acid, gatifloxacin and gemifloxacin (table III). Alatrofloxacin and enoxacin were associated with one ADR each – clonus and grand mal convulsion, respectively. In general, CNS adverse events developed within a few minutes or during the first days of treatment (1–8 days). Only one case developed after 5 months of chronic treatment with pefloxacin.[22]

In the majority of cases, patients recovered without sequelae, and normally the events disappeared on discontinuation of the drug.

For some CNS adverse events, such as delirium or psychosis, the majority of patients had no underlying diseases or concomitant medication that could induce/precipitate the development of delirium or psychosis. There were also cases showing positive dechallenge, where patients recovered within 1 day following drug withdrawal.[23-32] Moreover, the events developed within a few days after starting the quinolone. Concomitant factors were presented in some individual case reports of quinolone-induced seizures, as further discussed in section 4.

3.5 Ambulatory versus Hospital-Based Events

One hundred of 145 individual case reports (69.0%) had information on whether the event was ambulatory or hospital-based; 30 (20.7%) occurred when the patient was hospitalized and 70 (48.3%) occurred in outpatients (ambulatory care).

3.6 Seriousness

A serious ADR is any untoward medical occurrence that, at recommended dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Seventy (49.0%) individual case reports were identified as serious, with 2 (2.8%) being fatal, 14 (19.7%) prolonging the patient's hospitalization and 55 (77.5%) requiring inpatient hospitalization. None of the cases was life-threatening, resulted in disability/incapacity or was a congenital anomaly/birth defect. 51.0% of the individual case reports did not provide information on the seriousness criteria. One of the fatal events was probably related to an interaction between ciprofloxacin and theophylline. The patient had several concomitant diseases that cannot be ruled out as contributors.[54] The other fatal event was not related to ciprofloxacin administration, but was associated with the clinical condition of the

Table III. Overview of neurological and psychiatric adverse reactions reported with quinolones

MedDRA® PT[a,b]	CIP	OFL	PEF	LEV	NOR	NAL	GAT	GEM	ENO	ALA	Total no. of reactions [n (%)]
Abnormal dreams	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Absence seizure	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	1 (0.5)
Acute psychosis	8	NA	NA	NA	NA	NA	NA	NA	NA	NA	8 (3.9)
Ageusia	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Agitation	5	2	NA	NA	NA	NA	NA	NA	NA	NA	7 (3.4)
Agression	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Anticholinergic syndrome	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Anxiety	3	2	NA	NA	NA	NA	NA	NA	NA	NA	5 (2.4)
Anxiety disorder due to a general medical condition	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Ballismus	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Brain injury	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Catatonia	1	NA	NA	1	NA	NA	NA	NA	NA	NA	2 (1.0)
Cerebellar syndrome	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Chorea	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Clonic seizures	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	1 (0.5)
Clonus	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	1 (0.5)
Confusional state	4	3	2	NA	NA	NA	NA	NA	NA	NA	9 (4.4)
Convulsion	5	1	1	NA	NA	NA	1	NA	NA	NA	8 (3.9)
Delirium	4	NA	2	2	NA	NA	NA	NA	NA	NA	8 (3.9)
Delusion	NA	NA	NA	NA	1	NA	NA	NA	NA	NA	1 (0.5)
Depression	NA	1	NA	1	NA	NA	NA	NA	NA	NA	2 (1.0)
Dizziness	1	1	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Dysarthria	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Dyskinesia	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Dysphonia	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Dystonia	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	1 (0.5)
Electroencephalogram abnormal[c]	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Encephalopathy	NA	NA	NA	NA	NA	NA	NA	1	NA	NA	1 (0.5)
Epilepsy	1	1	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Euphoric mood	NA	2	NA	NA	1	NA	NA	NA	NA	NA	3 (1.4)
Extensor plantar response	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Extrapyramidal disorder	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Gait disturbances	NA	NA	NA	NA	NA	NA	1	NA	NA	NA	1 (0.5)

Continued next page

Table III. Contd

MedDRA® PT[a,b]	CIP	OFL	PEF	LEV	NOR	NAL	GAT	GEM	ENO	ALA	Total no. of reactions [n (%)]
Gaze palsy	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Grand mal convulsion	7	7	1	3	1	2	1	NA	1	NA	23 (11.2)
Grand mal seizure	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Grimacing	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Hallucination	1	1	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Hallucination, visual	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Hemiparesis	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Hostility	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Hyperkinesia	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Hyperacusis	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Insomnia	6	4	NA	NA	NA	NA	NA	NA	NA	NA	10 (4.9)
Irritability	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Mania	22	12	NA	NA	4	NA	NA	NA	NA	NA	38 (18.4)
Manic depression	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Mastication disorder	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Mood swings	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Muscle spasticity	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Myasthenia gravis	1	NA	NA	NA	1	NA	NA	NA	NA	NA	2 (1.0)
Myoclonus	3	1	1	NA	NA	NA	1	NA	NA	NA	6 (2.9)
Nervousness	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Neuropathy peripheral	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Nightmare	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Panic attack	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Paralysis	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Paranoia	NA	2	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Parosmia	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Partial seizures	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Personality disorder	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Polineuropathy	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Psychotic disorder	2	NA	NA	1	NA	NA	NA	NA	NA	NA	3 (1.4)
Psychotic disorder due to a general medical condition	NA	2	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Sedation	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Serotonin syndrome	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)

Continued next page

Table III. Contd

MedDRA® PT[a,b]	CIP	OFL	PEF	LEV	NOR	NAL	GAT	GEM	ENO	ALA	Total no. of reactions [n (%)]
Simple partial seizures	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Sleep disorder	NA	2	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Somatic delusion	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Suicidal ideation	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	1 (0.5)
Status epilepticus	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Tonic clonic jerking	NA	NA	NA	NA	NA	1	NA	NA	NA	NA	1 (0.5)
Toxic optic neuropathy	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Tourette's disorder	1	1	NA	NA	NA	NA	NA	NA	NA	NA	2 (1.0)
Tremor	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	1 (0.5)
Total no. of reactions per active substance (n)	**108**	**57**	**11**	**10**	**8**	**4**	**4**	**2**	**1**	**1**	**206**

a This table excluded the ADRs from the selected individual case reports belonging to other SOCs rather than 'Nervous system disorders' and 'Psychiatric disorders'. Percentages were calculated using the total of neurological and psychiatric ADRs.

b The ADRs were identified from references.[18-37,41,49-115]

c ADR 'Electroencephalogram abnormal' does not belong to the 'Nervous system disorders' or 'Psychiatric disorders', but was included in this table due to its relevance as a tool for the non-convulsive status epilepticus.

ADRs = adverse drug reactions; **ALA** = alatrofloxacin; **CIP** = ciprofloxacin; **ENO** = enoxacin; **GAT** = gatifloxacin; **GEM** = gemifloxacin; **LEV** = levofloxacin; **MedDRA®** = Medical Dictionary for Regulatory Activities; **NA** = not applicable; **NAL** = nalidixic acid; **NOR** = norfloxacin; **OFL** = ofloxacin; **PEF** = pefloxacin. **PT** = Preferred Term; **SOC** = System Organ Class.

patient.[41] A total of 78.9% of patients with a serious ADR recovered without sequelae from the CNS adverse reaction(s), while there is no information on outcome in 18.3% of the individual case reports.

When analysing these cases, there were no significant differences in the demographic characteristics of the patients. Similarly to that presented in section 3.2, more individual case reports of serious CNS adverse reactions refer to women than to men (64.3% vs 32.9%). Serious CNS adverse events developed more frequently in adults (57.7%) and elderly (35.2%) than in children/adolescents (5.6%). Ciprofloxacin, ofloxacin and pefloxacin were the quinolones responsible for the majority of the serious cases, consistent with what has been reported in section 3.4.

Eight of these serious individual cases were due to a possible interaction between the quinolone and theophylline (5 cases),[33,34,54,55] or with an NSAID (2 cases)[21,53] or methadone (1 case).[56] The description of adverse events and concomitant medication is detailed in section 3.7.

3.7 Concomitant Medication

Twenty-five individual case reports of neuropsychiatric ADRs due to the concomitant administration of a quinolone (ciprofloxacin, ofloxacin or pefloxacin) and theophylline, NSAID or other agents were identified (table IV). Seven individual case reports included NSAIDs, such as indomethacin, ibuprofen, aspirin (acetylsalicylic acid) and naproxen, while 12 reported an adverse event due to an interaction between a quinolone and theophylline. The majority of cases was related to ciprofloxacin (18 cases), followed by pefloxacin (4 cases) and ofloxacin (3 cases). Convulsion/seizures was the most common ADR following a drug interaction, while mania and delirium were reported in 2 cases each.

Seizures have also been reported with the concomitant administration of ciprofloxacin and foscarnet,[57] predicting a possible interaction between these two drugs. Drug interactions with vinca alkaloids[22] and chloroquine[58] have also been reported. Additionally, a possible interaction between ciprofloxacin and two potent serotonergic

Table IV. Summary of individual case reports regarding neurological and psychiatric adverse reactions due to interactions between quinolones and other agents

Suspected quinolone	Age (y)/ sex	Daily dose	Time to onset of reaction	Adverse reaction(s) [MedDRA® PT][a]	Clinical history	Concomitant medication[b]	Reference
Ciprofloxacin	74/F	200 mg q12h	24 hours	Grand mal seizure	Pulmonary TE	*Theophylline*	34
Ciprofloxacin	60/M	500 mg bid	NR	Grand mal convulsion	COPD, CAP	*Theophylline*	68
Ciprofloxacin	64/M	500 mg	8 hours	Grand mal convulsion	NR	*Indomethacin*, prednisolone, digoxin, glyburide, allopurinol	71
Ciprofloxacin	93/F	500 mg q12h	1 day	Convulsion	COPD, asthma	*Theophyllline*, ranitidine, prednisolone	72
Ciprofloxacin	88/M	500 mg bid	2 days	Delirium	Chronic epididymitis	*Ibuprofen*, heparin	25
Ciprofloxacin	57/F	500 mg bid	7 days	Grand mal convulsion	Metastatic breast cancer	*Theophylline*, tamoxifen	73
Ciprofloxacin	74/F	500 mg bid	3 days	Grand mal convulsion	Anorexia nervosa, gout, HTA	*Theophylline*	73
Ciprofloxacin	47/M	NR	NR	Delirium	NR	*Indomethacin*	23
Ciprofloxacin	68/F	500 mg bid	1 week	Polineuropathy	Mastectomy, collagenosis	*Naproxen*, *chloroquine*	58
Ciprofloxacin	46/M	500 mg	NR	Mania; aggression; agitation; anxiety	NR	*Ibuprofen*, lithium, amitriptyline	74
Ciprofloxacin	64/M	1000 mg	NR	Mania; psychotic disorder; nervousness	NR	*Acetylsalicylic acid (aspirin)*	74
Ciprofloxacin	39/M	750 mg q12h	At first administration of foscarnet	Grand mal convulsion	AIDS, PCP, candidiasis, disseminated MAC infection	*Foscarnet*, vancomycin, rifampin, clarithromycin, fluconazole, cimetidine, docusate sodium, morphine sulfate, calcium carbonate, magnesium oxide	57
Ciprofloxacin	38/M	750 mg q12h	36 hours	Grand mal convulsion	PCP, candidiasis, anaemia; hepatitis C, wasting syndrome, MAC infection	*Foscarnet*, ethambutol, pyrazinamide, rifampin, clofazimine	57
Ciprofloxacin	61/M	NR	NR	Serotonin syndrome	Chronic, non-malignant lower back pain, DM, MDD	*Venlafaxine*, *methadone,* hydromorphone, oxycodone	59

Continued next page

Table IV. Contd

Suspected quinolone	Age (y)/ sex	Daily dose	Time to onset of reaction	Adverse reaction(s) [MedDRA® PT][a]	Clinical history	Concomitant medication[b]	Reference
Ciprofloxacin	42/F	750 mg bid	2 days	Sedation[a]	Ogilvie's syndrome	*Methadone*, *venlafaxine* (only on the fourth occasion)	56
Ciprofloxacin	65/F	250 mg bid	NR	Epilepsy[a]	Left hemiplegia, atrial fibrillation; CCF, breast cancer	*Theophylline*, digoxin, bumetanide, tamoxifen	54
Ciprofloxacin	79/F	500 mg bid	24 hours	Anxiety disorder due to a general medical condition; agitation; confusional state[a]	COPD, CAD, MI	*Aminophylline*, terbutaline, prednisone, isosorbide dinitrate, meprobamate, furosemide, hydroxyzine, diphenhydramine	55
Ciprofloxacin	74/M	500 mg bid	1 day	Serotonin syndrome	HTA, cerebrovascular disease, depression, PBH	*Citalopram*, enalapril, aspirin, diazepam, reboxetine, sulpiride	66
Pefloxacin	NR/F	800 mg	2 days	Grand mal convulsion	Parkinson's disease, broncho-emphysema	*Theophyllline*, levodopa/benserazide	67
Pefloxacin	77/F	2800 mg	7 days	Grand mal convulsion	DM	*Theophylline*	33
Pefloxacin	31/F	2000 mg	4 days	Delirium	MMD	*Theophylline*	33
Pefloxacin	37/M	400 mg bid	5 months	Peripheral neuropathy	Chronic vertebral osteomyelitis recurrence with ofloxacin and ciprofloxacin	*Vincristine* (past drug therapy)	22
Ofloxacin	84/F	400 mg q12h	3 days	Convulsion	CAD, DJD, CVA, MI	*Pentoxifylline*, *aspirin*, furosemide, isosorbide dinitrate, famotidine	65
Ofloxacin	62/F	400 mg	NR	Grand mal convulsion	Asthma	*Theophyllline*, phosphomycine, netilmicine	70
Ofloxacin	63/F	NR	NR	Mania; paralysis	NR	*Aminophylline*, dihydrogesterone	74

a Only the ADRs belonging to the SOCs of interest are reported in this column. ADRs belonging to other SOCs are not mentioned.

b Italics represents the medicines that were responsible for the quinolone-drug interaction, leading to the neuropsychiatric ADR(s), being considered interacting agents.

ADRs = adverse drug reactions; **bid** = twice daily; **CAD** = coronary artery disease; **CAP** = community-acquired pneumonia; **CCF** = congestive cardiac failure; **COPD** = chronic obstructive pulmonary disease; **CVA** = cerebrovascular accident (stroke); **DJD** = degenerative joint disease; **DM** = diabetes mellitus; **F** = female; **HTA** = hypertension; **M** = male; **MAC** = *Mycobacterium avium* complex; **MDD** = major depressive disorder; **MedDRA®** = Medical Dictionary for Regulatory Activities; **MI** = myocardial infarction; **MMD** = myotonic muscular dystrophy; **NR** = not reported; **PBH** = prostate benign hypertrophy; **PCP** = *Pneumocystis carinii* pneumonia; **PT** = Preferred Term; **q12h** = every 12 hours; **SOCs** = System Organ Classes; **TE** = thromboembolism.

agents (methadone and venlafaxine) was reported, which manifested as serotonin syndrome or sedation.[56,59]

Two cases of neurological ADRs after the concurrent administration of two quinolones were reported: clonus after the administration of alatrofloxacin and ciprofloxacin;[35] and myoclonus after the administration of ofloxacin and pefloxacin.[20]

4. Discussion

A slightly higher number of psychiatric ADRs was reported among the overall individual case reports.

The majority of CNS adverse reactions induced by quinolones is related to their interaction with neurotransmitters, and partially due to their similarity in structure to GABA agonists. Quinolones may displace GABA from its receptors, decreasing GABAergic inhibition and leading to the stimulation of the CNS.[34,36,37,41] This stimulation results in epileptogenic neurotoxicity (e.g. seizures/convulsions). Binding to the GABA receptor is strongly influenced by the side chain in the 7-position of quinolones, as referred to in section 1.[1,6] *In vitro* data have demonstrated that the epileptogenic activity of quinolones is variable, being the degree of excitatory effect as follows (from the highest to the smallest effect): trovafloxacin > enoxacin > lomefloxacin > moxifloxacin > nalidixic acid > ciprofloxacin > ofloxacin. No data were available for norfloxacin or levofloxacin.[6,41] Trovafloxacin was rated as having the highest epileptogenic activity, while pefloxacin is associated with the fewest CNS adverse reactions, despite the greatest CNS penetration.[40,41] No individual case reports were identified for trovafloxacin, which might be due to its earlier withdrawal from the market. Levofloxacin has the lowest CNS penetration,[14,16,38] and therefore a lower rate of neurotoxicity. Ciprofloxacin, ofloxacin and pefloxacin are known to cross the BBB to a moderate extent in the presence of inflamed meninges,[12,13,43] which may be one of the reasons for the increased number of CNS adverse events identified in this review for these three drugs (despite the seriousness of some cases). However, none of the individual case reports described the use of these quinolones for the treatment of meningitis. CNS penetration of quinolones plays an important role in determining the relative frequency and severity of CNS toxicity,[13] but the relationship between the incidence of these ADRs and the CNS pharmacokinetics of quinolones remains unclear.[12,13,43,45]

Additionally, ciprofloxacin has been extensively used worldwide (marketed since 1987)[12,13] due to its safety and tolerability profiles; therefore, the frequency of exposure to this fluoroquinolone may account for the number of ADRs reported in the literature and identified in this review. As cited by Heyd and Haverstock,[116] among a total of 63 059 patients treated with oral ciprofloxacin in clinical trials, adverse events occurred in 5.8% of adult patients, with 1.1% being CNS-related events. Ofloxacin and pefloxacin have not been used to the same extent as ciprofloxacin and, therefore, the number of CNS adverse reactions identified for ofloxacin and pefloxacin may be over-representative which is consistent with post-marketing surveillance reports.[26] Moreover, ofloxacin has been associated with sleep disturbances, confusion, psychiatric disorders and convulsion in the past,[15] which could have potentiated the increased number of reports related to this drug, as healthcare professionals may be more aware of these events than of more common and familiar complaints. Among the modern fluoroquinolones, levofloxacin, the left optical isomer of ofloxacin, has an overall incidence of CNS adverse effects of 0.2–1.1% (overall adverse effects 2–10%).[15] This drug is associated with considerably fewer CNS adverse reactions when compared with ofloxacin. The underlying reason for this difference is the influence of the R(+) isomer of ofloxacin, which may contribute to the ADR profile of levofloxacin.[13,117,118] Contrary to expectations, no individual case reports were identified for lomefloxacin, yet it has been associated with a high incidence of tremor, seizures and dizziness.[15,117] In a review by Bertino and Fish,[117] the rate of reported seizures was approximately 45 per million prescriptions of lomefloxacin, compared with 10 per million prescriptions with ciprofloxacin, ofloxacin or norfloxacin together.

Seizures and other neurological events have been reported worldwide with nalidixic acid and several fluoroquinolones. Seizures/convulsions were one of the most common CNS adverse reactions identified in this review for quinolones, despite the rarity of overall CNS adverse reported in the literature with this class of drugs. Seizures are a rare ADR of ciprofloxacin,[119] while the Summary of Product Characteristics (SPC) for ofloxacin reports this event as very rare (<0.01%).[120] The number of reports of seizures/convulsions may be due to the seriousness or severity of such events, as well as their clinical significance. They may be precipitated by several factors, such as sleep deprivation, malformations, head injuries, infections, metabolic disturbances, multiple sclerosis and drugs.[121] The main mechanism underlying this adverse event is the inhibition of GABA by quinolones, as mentioned earlier. Other mechanisms have been proposed, such as the involvement of the dopamine receptor[60] and the agonist effect of fluoroquinolones on the glutamate receptor NMDA.[61] Fluoroquinolones are thought to activate NMDA channels by chelating with magnesium and removing its channel blocking effect.[60]

Possible contributing factors to the development of several types of seizures and convulsions in patients taking quinolones may be a history of seizures or epilepsy,[35,36,62,63] electrolytic disturbances,[35,41,64,65] concomitant medication,[23,25,33-36,54-56,58-59,63,66-74] history of renal[21,60,69,75,76] and/or hepatic failure,[53,75] increased age[35,60,64,77] and excessive dosages.[35,52,53] Moreover, these factors not only contribute to the development of seizures, but also to some psychiatric events induced by quinolones, which were mentioned in section 3.4.

Dosage is an important contributing factor to the development of seizures because they have been reported in children after the ingestion of excessive doses of nalidixic acid.[18,51] Other cases showed that fluoroquinolones were administered at excessive dosages, indicating that no dose adjustments were made in patients with renal[20,21,52] or hepatic[53] disease. Caution is recommended and required in patients with co-morbidities, as well as dose adjustments to avoid the neurotoxicity of quinolones. Nevertheless, quinolones may induce seizures even at therapeutic dosages because we have identified only seven cases of overdose and excessive dosage in this review.

The concomitant administration of theophylline and NSAIDs is another contributing factor to quinolone-induced seizures. In the presence of a quinolone, the serum concentration of theophylline increases about 20% and its clearance decreases about 30%;[34,67,70,73] therefore, the dose of theophylline should be reduced when a quinolone is started as the threshold for seizures is lowered. In addition to seizures, visual hallucinations have been reported in patients using multiple drug therapy, including theophylline.[30] Ciprofloxacin, as well as theophylline is metabolized by cytochrome P450 (CYP); therefore, the interaction between these two drugs is likely to occur in the liver via CYP.[72] This is not a class effect as the affinity of each quinolone for CYP varies. According to published data, fluoroquinolones are ranked as follows with regard to interaction with theophylline (from the greatest to the smallest effect): enoxacin (also inhibits CYP)[55] > ciprofloxacin > norfloxacin > ofloxacin, levofloxacin, trovafloxacin, gatifloxacin, moxifloxacin.[13] It has also been shown that position 1 influences theophylline interaction, the most marked effects being with enoxacin, ciprofloxacin and pefloxacin.[78] Indeed, several cases of ADRs following interactions between theophylline and ciprofloxacin or pefloxacin have been reported (table IV). Contrary to expectation, no individual case reports for an enoxacin-theophylline interaction were identified in this literature review.

The decrease in renal blood flow due to the inhibition of prostaglandins, as a result of NSAID activity, may increase the quinolone concentration, predisposing patients to ADRs. As ciprofloxacin is mainly eliminated by renal excretion, its elimination may be impaired by NSAID activity.[58] Also, the potentiation by NSAIDs of the competitive inhibition of neuronal GABA receptors by quinolones (by up to 30 000 times) may induce these types of drug interactions and, consequently, the development of neurotoxicity.[13,79] Shimada and Hori[80] demonstrated that fluoro-

quinolones may induce seizures at lower concentrations when administered concomitantly with NSAIDs.[80] This is consistent with the results presented in this review. Additionally, the structure at the 7-position of the quinolone influences the risk of NSAID-potentiated CNS events. Fluoroquinolones with unsubstituted piperazinyl rings (e.g. ciprofloxacin) have a stronger interaction with NSAIDs.[6] The rank order of inhibitory effects of the fluoroquinolones was as follows (from the highest to the smallest effect) prulifloxacin, norfloxacin > ciprofloxacin ≥ enoxacin > gatifloxacin ≥ ofloxacin, tosufloxacin, lomefloxacin > levofloxacin ≥ sparfloxacin ≥ pazufloxacin. No data were provided for pefloxacin. Fenbufen, flurbiprofen and ketoprofen, among various NSAIDs, have been reported to potently enhance the convulsive activity of fluoroquinolones and, consequently, inhibition of the GABA current by quinolones. A weaker potentiation was seen with diclofenac, zaltoprofen and loxoprofen. Oxicam derivates, such as tenoxicam and piroxicam, do not act as potentiators of the convulsive activity of quinolones.[81] Quinolone-NSAID interactions discussed in this review did not occur with any of the NSAIDs mentioned above.

The previous drug interactions are the most common and the most reported in the literature, as shown in table IV. In this literature review we also described other fluoroquinolone drug interactions, such as those with antivirals, antihistamines, vinca alkaloids, antidepressants, opiate analgesics, and antimalarial and antineoplastic drugs. The administration of chloroquine, an antimalarial drug capable of inducing seizures, in patients with a low seizure threshold precipitates the development of seizures. The underlying mechanism for this pharmacokinetic interaction may be the role of CYP, as both chloroquine and ciprofloxacin are metabolized via CYP enzymes. This interaction reported by Rollof and Vinge[58] did not result in seizures but in polyneuropathy. The concurrent administration of ciprofloxacin and two potent serotonergic agents (venlafaxine and methadone) may also induce CNS adverse reactions, identified in two individual case reports.[56,59] The concurrent administration of ciprofloxacin and both methadone and venlafaxine led to the development of serotonin syndrome in one case,[59] while in the other the patient became sedated following the addition of ciprofloxacin to methadone.[56] Ciprofloxacin was reintroduced three times, and the patient became sedated on all occasions. Additionally, on the last occasion, venlafaxine had been replaced by fluoxetine.[56] Both methadone and venlafaxine are metabolized by CYP isoenzymes (CYP1A2 for methadone only, and CYP3A4 for methadone and venlafaxine). Ciprofloxacin is a known potent inhibitor of CYP1A2 and depresses CYP3A4 in human hepatic microsomes; therefore, a pharmacokinetic interaction involving ciprofloxacin, methadone and/or venlafaxine may be responsible for the neurotoxicity of quinolones.[56,59] Interestingly, Montané et al.[66] reported a case of serotonin syndrome induced by several drug interactions, involving antidepressants and ciprofloxacin. Serotonin syndrome first developed when the patient added reboxetine to fluoxetine and then when switched from fluoxetine to citalopram. Despite the pharmacokinetic and pharmacodynamic interactions involved in this case, the addition of ciprofloxacin could have also contributed to serotonin syndrome resulting in a pharmacokinetic interaction between ciprofloxacin and citalopram. CYP3A4, inhibited by ciprofloxacin, is involved in the metabolism of citalopram, leading to an increased plasma concentration of this drug. The participation of ciprofloxacin in serotonin syndrome is less likely,[66] but this drug interaction should be considered when prescribing a quinolone to a patient receiving antidepressant treatment. Peripheral neuropathy following administration of pefloxacin and subsequent administrations of ofloxacin and ciprofloxacin was reported. As the patient had been exposed in the past to vinca alkaloids, known neurotoxic drugs, Aoun et al.[22] suggested that vinca alkaloids might potentiate fluoroquinolone-induced peripheral neuropathy. Another drug interaction that may enhance the risk of seizures is between foscarnet, an antiviral drug, and epileptogenic agents (e.g. fluoroquinolones). Foscarnet is known to induce seizures; the concomitant administration of ciprofloxacin may enhance the development of

seizures by an unknown mechanism.[57] An ofloxacin overdose potentiated the anticholinergic effect of diphenhydramine and chlormezanone when these three drugs were administered concurrently.[19]

Although the convulsive potential of quinolones may also be related to their chemical structures, there are no established data on their cross-reactivity. Melvani and Speed[35] reported a case of alatrofloxacin-induced clonus. Alatrofloxacin, a pro-drug of trovafloxacin,[7] was administered on the same day as the last two doses of oral ciprofloxacin. On the other hand, Bagon[20] reported a case of myoclonus and muscle spasticity in an elderly patient with renal failure to whom ofloxacin and pefloxacin were administered. Data on cross-reactivity of quinolones are scarce, yet in both cases patients developed neurological ADRs. The concurrent administration of two quinolones[20,35] might have increased the risk of seizures because of a higher threshold reduction. Further studies are required to investigate the possibility of cross-reactivity between quinolones.

An electrolyte disturbance may also contribute to the epileptogenic activity of quinolones. Seizures may occur with hypernatraemia,[65] hypomagnesaemia[41] and hyponatraemia.[35,41,64] Hypomagnesaemia is associated with neuronal irritability; therefore, the administration of a quinolone triggers seizures more easily.[41] Uraemic patients may accumulate the quinolone or its metabolite, precipitating convulsions, of which pefloxacin[69] was an example. Pefloxacin presents high serum levels and undergoes biotransformation, leading to the accumulation of the drug itself or its metabolite in patients with renal or hepatic diseases, and therefore increasing the risk of seizures.[75] In the case of ofloxacin, its elimination is highly dependent on renal excretion, requiring dosage adjustments in patients with renal impairment.[65]

Elderly patients are prone to develop seizures and other neuropsychiatric adverse events (such as delirium and psychosis) because of pharmacodynamic changes that occur with increased age. These changes include alterations in volume of distribution, drug metabolism and elimination, and protein binding.[82] Elderly patients should be closely monitored when prescribing a quinolone, especially if they have CNS impairments, multiple co-morbidities or are taking other medicines. There does not seem to be a high-risk group for the development of neurotoxicity, at least according to our results (31.7% of individual case reports occurred in elderly patients) and without other precipitating factors. These results are consistent with the conclusions of Stahlmann and Lode.[83]

Alcohol dependence is a known risk factor for seizures, which may occur until 2 days after stopping drinking. Lahmek et al.[84] reported a case of ofloxacin-induced seizures in a patient undergoing detoxification for alcohol dependence. Ofloxacin was considered the most probable cause rather than alcohol dependence because the patient stopped drinking 7 days prior to seizures. Additionally, the patient was taking venlafaxine but there are no reports of drug interactions between ofloxacin and venlafaxine to date. Patients treated with benzodiazepines have a higher risk of seizures, due to a possible interaction of ofloxacin with the benzodiazepine-binding sites located on the same complex as the GABA receptor site. There might be a displacement of GABA from its receptor, decreasing GABAergic inhibition.[84] Akaike et al.[122] showed contradictory findings: the inhibitory actions of fluoroquinolones combined with biphenyl acetic acid on GABA-mediated response were not influenced by the presence of flumazenil, a benzodiazepine antagonist.

Agbaht et al.[85] reported a case of grand mal convulsion associated with ciprofloxacin in a patient with underlying thyrotoxicosis. This disease lowers the threshold of epileptiform activity, and may therefore cause seizures. Thyrotoxicosis may be considered a risk factor for quinolone-induced seizures.

Psychiatric adverse effects are rare, albeit serious. They seem to be dose-dependent and directly related to the quinolone concentration at the receptor site. The underlying mechanism involves GABA inhibition, as mentioned above;[29,86] however, the mechanism by which quinolone-induced delirium remains unclear. Despite GABA involvement, it is possible that the development of quinolone-induced non-convulsive status

epilepticus may potentiate some psychotic ADRs (e.g. delirium). Isolated cases of abnormal EEG have been reported, which may be a tool to exclude quinolone-induced non-convulsive status epilepticus.[26] Contrary to the majority of psychiatric adverse effects, dizziness is not a rare event in patients taking quinolones. However, it has only been reported in two cases (ciprofloxacin and ofloxacin),[74] probably because it is not a serious and uncommon adverse event and does therefore not require the attention of healthcare professionals and thus reporting. Prescription Event Monitoring in the UK[123] showed lower rates of dizziness with ciprofloxacin, norfloxacin and ofloxacin. Moreover, the Swedish database (Sweweb)[124] had reports of dizziness only with ciprofloxacin.

Several cases of psychosis,[27-31,49,87-89] delirium,[24-26,32,90,91] mania[74,92] and hallucinations[34,74] have been reported, mainly with ciprofloxacin and ofloxacin, despite their rarity. We believe that these events were commonly reported in the literature because of their seriousness (they can progress to self-endangering, being life-threatening or even fatal), severity and providing new information at the time of the report. Additionally, as mentioned earlier, CNS adverse events may be over-represented because the characteristics of these events are well known by healthcare professionals, as they are more frequently reported than common gastrointestinal events or dizziness and headache (the most common CNS adverse effects listed in the SPCs of several quinolones).[93,119,120,125-126] A large, retrospective, 5-year study showed that psychiatric adverse events associated with fluoroquinolones occurred in 0.015% of inpatients.[89] Insomnia has been reported in about 4.7% of patients treated with ofloxacin, while psychosis occurs in <1% of patients.[13,93,119,120,125,126] Therefore, reports of insomnia are expected with quinolones, as well as delirium and psychosis. Insomnia has also been reported to the French database (2006) as a common ADR (8%).[93] Delirium and psychosis may also result from a quinolone-drug interaction (table IV); however, for the majority of cases identified in this review, there was no precipitating factor for the development of such CNS adverse events.

An isolated case of an acute psychotic reaction following the use of topical ciprofloxacin (one eyedrop every hour) in a young woman was reported by Tripathi et al.[49] This ADR was suspected to be idiosyncratic, aided by the increased systemic absorption of ciprofloxacin secondary to the severe eye inflammation. A second case of neurotoxicity following topical administration of ciprofloxacin was identified by Orr and Rowe.[50] In this case, several episodes of grand mal convulsions following the intermittent prescription of ciprofloxacin eardrops was reported.[50] No other cases of ADRs following topical administration of ciprofloxacin or any other quinolone were identified. In fact, it is important to take into consideration that topical medication, despite being frequently omitted from medical histories, can produce systemic effects, especially where there are precipitating factors such as concomitant drugs, previous psychiatric disturbances, alcohol abuse and epileptogenic predisposition.

A case of delusional parasitosis due to ciprofloxacin, apparently the first such case report, has been reported in the literature.[94] Hallucinations, which can be a symptom of psychosis, are rare among patients taking only fluoroquinolones, but are frequent in patients using multiple drugs, with a quinolone being one of them. An analysis of the Swedish database, Sweweb,[124] showed a small number of reports of hallucinations after ciprofloxacin and levofloxacin administrations.

Antibacterials are believed to be associated with mania, despite being a rare event and affecting individuals in an unpredictable way, as cited by Abouesh et al.[74] In total, 40 cases of fluoroquinolone-induced mania have been reported worldwide,[74,90] and this is the most common psychiatric ADR reported with fluoroquinolones (mainly with ciprofloxacin, ofloxacin and norfloxacin), even though the SPCs of quinolones do not list this clinically significant adverse event.[119,120,125,126] Mania symptoms in some patients, as discussed by Abouesh et al.,[74] may be idiosyncratic, unless the patient has had a history of personality disorders or psychosis, which put them at a higher risk of developing

mania.[74,92] Several mechanisms have been proposed for antibacterial-induced mania, but with reference to quinolones, GABA inhibition is the agreed mechanism. James and Demian[31] suggested that sepsis or brain injury/trauma may also be contributing factors. Because of the characteristics of mania reactions (seriousness and consequences/outcome), these events are more frequently reported by healthcare professionals than other events. In addition, Abouesh et al.[74] presented an overview of spontaneous reports to WHO and US FDA databases, which increases the number of known reports.

A variety of hyperkinetic movement disorders have been described after the administration of quinolones, especially ciprofloxacin. Among them, tremor is a rare event,[119,120] which is consistent with the number of reports published (one case).[95] Other abnormal movements included grimacing,[96] chorea,[97] dyskinesia,[94,98] Tourette-like syndrome,[99,100] propriospinal myoclonus[101] and dystonia.[60] Of those, movement disorders are listed in the US SPC for ciprofloxacin[119] and other quinolones.[120,125,126] These events have been reported mainly in the elderly and in patients with liver or renal diseases, which is consistent with the predisposing factors for neuropsychiatric ADRs induced by quinolones. Dyskinesia was reported even in patients with slight changes in liver metabolism.[99] Subclinical hepatocerebral degeneration might also be a precipitating factor for grimacing and dyskinesias.[98] The emergence of psychosis and Tourette-like manifestations suggests that quinolones might have some central dopaminergic action as dopaminergic mechanisms are involved in the genesis of Tourette's syndrome. GABA antagonism in the basal ganglia may disinhibit dopaminergic mechanisms.[99,100] This evidence was supported in a mouse model where haloperidol protected against quinolone-induced seizures.[100]

Gait disturbances associated with gatifloxacin have been reported[102] despite being a listed event for some fluoroquinolones.[93,119,120,125,126] Hemiparesis, accompanied by dysarthria and dysphonia following the administration of ciprofloxacin was reported in an adolescent. The patient was positively rechallenged, i.e. a new episode of hemiparesis occurred. This case suggests a vascular mechanism affecting the brain system.[103] Hemiparesis is not listed in the US SPC for ciprofloxacin[119] or any other quinolone.[120,125,126] Sleep disorders, nightmares and insomnia were identified in children aged 6 and 10 years.[103] Patients taking a recommended dose of ofloxacin complained of sleep disturbances. In two case reports, the symptoms resolved after ofloxacin suspension and did not reoccur once a new quinolone was introduced.[104] These reports are consistent with the information collected from Sweweb,[124] despite being rare.[126] Although these events seem to be common in children, no special warnings are listed in the US SPC of ofloxacin.[125]

Catatonic syndrome has been reported as a complication of thyphoid fever, but the involvement of ciprofloxacin in a patient being treated for thyphoid fever remains uncertain and no clear causal relationship can be made.[105] Recently, catatonia was reported following the administration of levofloxacin.[106] The underlying hypotheses suggest that catatonia is due to a dysregulation of the dopaminergic neurotransmission or the GABAergic neurotransmission, with the dysregulation of the GABAergic neurotransmission being the most consensual hypothesis.[106] The administration of quinolones to patients where neuromuscular transmission has already been affected can aggravate or unmask myasthenia gravis. Possible exacerbation of myasthenia gravis has been reported with several quinolones. This review identified two cases of exacerbation of myasthenia gravis after the administration of norfloxacin[107] and ciprofloxacin.[108] More recently, the FDA warned that fluoroquinolones should be avoided in patients already experiencing myasthenia gravis because of their neuromuscular blocking activity and thus the exacerbation of muscle weakness.[6,107,108,127]

Despite the majority of quinolones being withdrawn from the market or their use being restricted, no major differences in their CNS adverse reaction profile were identified. Because of a worldwide use of ciprofloxacin, we found more individual case reports associated with this drug than with other quinolones, which was expected. Levofloxacin, also used worldwide, has fewer

neuropsychiatric ADRs due to the lowest CNS penetration. Levofloxacin also has a low potential for interaction with CYP, minimizing the risk of drug interactions and allowing it to be an option in polypharmacy. Several CNS adverse reactions were also identified for ofloxacin and pefloxacin, which may be over-representative as these drugs are used in a less extent than ciprofloxacin. In terms of the events themselves, the types of events seen comparing different quinolones was consistent and similar from one quinolone to the other.

The results from the literature review showed that about half of the individual case reports were serious, with the majority of them being associated with hospitalization or prolongation of the existing hospitalization. The other half provided no information on the seriousness of the case but we consider that these case reports indicated an event sufficiently serious and/or unexpected to be reported in the worldwide literature and therefore clinically relevant/significant. Moreover, the cases occurred mainly in patients in ambulatory care rather than inpatients and this is consistent with the therapeutic uses/indications of quinolones.

This literature review has some limitations regarding how subjective the selection of articles was. The limitations were mainly due to the methodology used to conduct the review, which excluded clinical trials and observational studies. This was because the aim of the study was to identify case reports and case series from the literature and to characterize the CNS adverse reaction profile of quinolones based on case reports and case series. Because of the information that can be retrieved from clinical trials, an important bias was introduced in this review. Additionally, the quality of the case reports, the lack of completeness and detailed information of the individual case reports may also introduce bias. The bias was minimized by using the guidelines for submitting adverse events reports for publication,[48] which helped us to collect the most appropriate information from each identified case report/case series, increasing the quality of the information retrieved. Several reports were published prior to those guidelines (prior to 2007), which decreased the amount of information available, clarity and quality of the earlier case reports. The information retrieved from the literature may be an important pharmacovigilance tool, especially in the evaluation of the safety profile of a drug and the benefit-risk analysis. The lack of information on the reported ADRs at the time of publication of the articles included in our review meant we could not evaluate the impact of such publications in the SPCs of the marketed quinolones. As we could not retrieve the history of the SPCs, especially those at the time of publication of the articles, we do not have accurate information as to whether the event was labelled or not at that time or if it was included in the SPCs after publication. Due to the absence of information on patient exposure, it was not possible to evaluate/estimate the frequency of these ADRs.

5. Conclusions

The results of our review showed that the majority of CNS adverse reactions was expected for quinolones, in particular for ciprofloxacin. Ciprofloxacin, ofloxacin and pefloxacin were the quinolones with more neurological and psychiatric ADRs reported in the literature. Ciprofloxacin has been extensively used worldwide, which may explain the observed pattern of ADRs, while for ofloxacin and pefloxacin, the number of reports may be over-represented.

Mania, the most reported event, is not included in the SPC of quinolones; however, due to the high number of reports, the need for its inclusion in the SPCs should be evaluated by the manufacturers, and the underlying mechanism clarified. Literature searches such as this are a known pharmacovigilance tool, which can be used in updating SPCs.

Patients with underlying medical conditions or receiving concomitant medication may be at higher risk of developing neuropsychiatric ADRs; however, these events may also occur in 'healthy' patients. One factor that should be further investigated is a possible cross-reactivity between quinolones.

Several factors should be taken into account when explaining CNS adverse effects, such as CNS

penetration, chemical structure of the quinolone and the convulsive activity of each quinolone. Although these factors have been identified, the propensity of individual quinolones to cause convulsions is unclear and further research is warranted.

Acknowledgements

The authors would like to thank Liliana Coelho, assistant at the Medical Department, Grupo Tecnimede, for her support and assistance with retrieving full-text articles.

Both authors are full-time employees of Grupo Tecnimede, which markets some fluoroquinolones (ciprofloxacin, levofloxacin, lomefloxacin and ofloxacin) in some European and non-European countries. No sources of funding were used to assist in the preparation of this review.

References

1. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. Ann Pharmacother 2007; 41: 1859-66
2. Zhanel GH, Noreddin AM. Pharmacokinetics and pharmacodynamics of the new fluoroquinolones: focus on respiratory infections. Curr Opin Pharmacol 2001; 1 (5): 459-63
3. Blondeau JM. Fluoroquinolones: mechanism of action, classification, and development of resistance. Surv Ophthalmol 2004; 49 Suppl. 2: S73-8
4. Melhus A. Fluoroquinolones and tendon disorders. Expert Opin Drug Saf 2005; 4 (2): 299-309
5. Lewis RJ, Mohr III JF. Dysglycaemias and fluoroquinolones. Drug Saf 2008; 31 (4): 283-92
6. Dukes MNG, editor. Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions: fluoroquinolones. 15th ed. Amsterdam: Elsevier Science, 2006: 1396-407
7. Sprandel KA, Rodvold KA. Safety and tolerability of fluoroquinolones. Clin Cornerstone 2003; 5 Suppl. 3: S29-36
8. Smith DA, Schmid EF. Drugs withdrawals and the lessons within. Curr Opin Drug Discov Devel 2006; 9 (1): 38-46
9. Rubinstein E. History of quinolones and their side effects. Chemotherapy 2001; 47 Suppl. 3: 3-8
10. European Medicines Agency. EMEA restricts use of oral norfloxacin drugs in UTIs. London: European Medicines Agency, 2008 Jul 24
11. European Medicines Agency (EMEA), Danish Medicines Agency. EMEA recommends restricting the use of oral moxifloxacin-containing medicines. London: European Medicines Agency, 2008 Jul 24
12. Owens Jr RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005; 41 Suppl. 2: S144-57
13. Fish DN. Fluoroquinolone adverse effects and drug interactions. Pharmacotherapy 2001; 21 (10 Pt 2): 253-72S
14. Sweetman SC, editor. Martindale: the complete drug reference. 33rd ed. London: Pharmaceutical Press; 2002: 113, 182-6, 201, 209, 219-20, 232; 248, 266-7
15. Ball P. Adverse drug reactions: implications for the development of fluoroquinolones. J Antimicrob Chemother 2003; 51 Suppl. 1: 21-7
16. Rodvold KA, Neuhauser M. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Pharmacotherapy 2001; 21 (10 Pt 2): 233-52S
17. Perry CM, Barman Balfour JA, Lamb HM. Gatifloxacin. Drugs 1999 Oct; 58 (4): 683-96; discussion 697-8
18. Jo M, Tachi N, Shinoda M. Convulsions from excessive dosage of nalidixic acid: a case report. Brain Dev 1979; 1: 327-9
19. Koppel C, Hopfe T, Menzel J. Central anticholinergic syndrome after ofloxacin overdose and therapeutic doses of diphenhydramine and chlormezanone. J Toxicol Clin Toxicol 1990; 28: 249-53
20. Bagon JA. Neuropsychiatric complications following quinolone overdose in renal failure [letter]. Nephrol Dial Transpl 1999; 14: 1337
21. Tattevin P, Messiaen T, Pras V, et al. Confusion and general seizures following ciprofloxacin administration. Nephrol Dial Transplant 1998; 13: 2712-3
22. Aoun M, Jacquy C, Debusscher L, et al. Peripheral neuropathy associated with fluoroquinolones [letter]. Lancet 1992; 340: 127
23. Orón JD, Ivorra J, Portilla J, et al. Reacción psicótica tras la administración de indometacina y ciprofloxacino [letter]. Rev Clin Esp 1992; 191: 401
24. Altés J, Gascó J, Antonio J, et al. Ciprofloxacin and delirium. Ann Intern Med 1989; 110: 170-1
25. McDermott JL, Gideonse N, Campbell JW. Acute delirium associated with ciprofloxacin administration in a hospitalized elderly patient. J Am Geriatr Soc 1991; 39: 909-10
26. Kiangkitiwan B. Levofloxacin-induced delirium with psychotic features. Gen Hosp Psychiatry 2008; 30 (4): 381-3
27. Reeves RR. Ciprofloxacin-induced psychosis. Ann Pharmacother 1992; 26: 930-1
28. Meher LK, Tripathy D, Acharya S. Ciprofloxacin induced psychosis. J Assoc Physicians India 1992; 40: 418-9
29. Mulhall JP, Bergmann LS. Ciprofloxacin-induced acute psychosis. Urology 1995; 46 (1): 102-3
30. Zaudig M, von Bose M, Weber MM, et al. Psychotoxic effects of ofloxacin. Pharmacopsychiatry 1989; 22: 11-5
31. James E, Demian A. Acute psychosis in a trauma patient due to ciprofloxacin. Postgrad Med J 1998; 74: 189-90
32. Hakko E, Mete B, Ozaras R, et al. Levofloxacin-induced delirium [letter]. Clin Neurol Neurosurg 2005; 107 (2): 158-9
33. Andrejak M, Schmit JL, Tondriaux A, et al. Neurological side effects of fluoroquinolones: apropos of 9 cases concerning pefloxacin [in French]. Therapie 1992; 47 (5): 415-8
34. Asensio-Sánchez VM, Rodríguez-Delgado B, García-Herrero E, et al. Visual hallucinations secondary to ciprofloxacin treatment. Arch Soc Esp Oftalmol 2007; 82 (5): 299-301
35. Melvani S, Speed BR. Alatrofloxacin-induced seizures during slow intravenous infusion. Ann Pharmacother 2000; 34: 1017-9

36. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. Ann Pharmacother 2004; 38: 235-7
37. Isaacson SH, Carr J, Rowan AJ. Ciprofloxacin-induced complex partial status epilepticus manifesting as an acute confusional state. Neurology 1993; 43: 1619-21
38. Wimer SM, Schoonover L, Garrison MW. Levofloxacin: a therapeutic review. Clin Ther 1998; 20 (6): 1049-70
39. Balfour JA, Wiseman LR. Moxifloxacin. Drugs 1999 Mar; 57 (3): 363-73; discussion 374
40. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones: an overview on mechanistic aspects. Curr Med Chem 2001; 8 (4): 371-84
41. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother 2001; 35 (10): 1194-8
42. Oliphant CM, Green GM. Quinolones: a comprehensive review. Am Fam Physician 2002; 65 (3): 455-64
43. Turnidge J. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs 1999; 58 Suppl. 2: 29-36
44. Tamai I, Yamashita J, Kido Y, et al. Limited distribution of new quinolone antibacterial agents into brain caused by multiple efflux transporters at the blood-brain barrier. J Pharmacol Exp Ther 2000; 295 (1): 146-52
45. Mandell L, Tillotson G. Safety of fluoroquinolones: an update. Can J Infect Dis 2002; 13 (1): 54-61
46. Case report [online]. Available from URL: http://en.wikipedia.org/wiki/Case_report [Accessed 2010 Sep 8]
47. ICH E2E: pharmacovigilance planning. CPMP/ICH/5716/03 [online]. Available from URL: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html [Accessed 2010 Sep 8]
48. Kelly WN, Arellano FM, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Drug Saf 2007; 30 (5): 367-73
49. Tripathi A, Chen SI, O'Sullivan S. Acute psychosis following the use of topical ciprofloxacin. Arch Ophthalmol 2002; 120: 665-6
50. Orr CF, Rowe DB. Eardrops attacks: seizures triggered by ciprofloxacin eardrops. Med J Aust 2003; 178: 343
51. Islam MA, Sreedharan T. Convulsions, hyperglycemia and glycosuria from overdose of nalidixic acid. JAMA 1965; 192: 1100-1
52. Schwartz MT, Calvert JF. Potential neurological toxicity related to ciprofloxacin. DICP 1990; 24 (2): 138-40
53. Kim SH, Jeong SH, Kim JW, et al. A case of hemiballism as a rare side effect of ciprofloxacin in a patient with liver cirrhosis. Chemotherapy 2009; 55: 207-10
54. Holden R. Probable fatal interaction between ciprofloxacin and theophylline [letter]. BMJ 1988; 297: 1339
55. Spivey JM, Laughlin PH, Goss TF, et al. Theophylline toxicity secondary to ciprofloxacin administration. Ann Emerg Med 1991; 20: 1131-4
56. Herrlin K, Segerdahl M, Gustafsson LL, et al. Methadone, ciprofloxacin, and adverse drug reactions. Lancet 2000; 356: 2069-70
57. Fan-Havard P, Sanchorawala V, Oh J, et al. Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. Ann Pharmacother 1994; 28: 869-72
58. Rollof J, Vinge E. Neurological adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. Ann Pharmacother 1993; 27: 1058-9
59. Lee J, Franz L, Goforth HW. Serotonin syndrome in a chronic-pain patient receiving concurrent methadone, ciprofloxacin, and venlafaxine [letter]. Psychosomatics 2009; 50 (6): 638-9
60. Sharma DD, Aggarwal A, Sharma RC, et al. A probable association of acute dystonia with gemifloxacin administration. Indian J Med Sci 2009; 63 (12): 557-60
61. Christie MJ, Wong K, Ting RH, et al. Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. Ann Pharmacother 2005; 39 (5): 953-5
62. Simpson KJ, Brodie JR. Convulsions related to enoxacin [letter]. Lancet 1985; II: 161
63. Poe TE, Marion GS, Jackson DS. Seizures due to nalidixic acid therapy. South Med J 1984; 77: 539-40
64. Anastasio GD, Menscer D, Little JM. Norfloxacin and seizures [letter]. Ann Intern Med 1988; 109: 169-70
65. Traeger SM, Nonfiglio MF, Wilson JA, et al. Seizures associated with ofloxacin therapy. Clin Infect Dis 1995; 21 (6): 1504-6
66. Montané E, Barriocanal A, Isern I, et al. Multiple drug interactions – induced serotonin syndrome: a case report. J Clin Pharm Ther 2009; 34: 485-7
67. Conri C, Lartigue MC, Abs L, et al. Convulsions chez une malade traitée par péfloxacine et théophylline [letter]. Thérapie 1990; 45: 358
68. Bader MB. Role of ciprofloxacin in fatal seizures. Chest 1992; 101: 883-4
69. Romano C, Cristina T, Daniela C, et al. Epileptic attacks associated with pefloxacin treatment in a patient on CAPD [letter]. Clin Nephrol 1989; 32: 48-9
70. Bercault N, DeMasure M, Benhamou CL, et al. Seizures in the course of prolonged treatment with ofloxacin. Rev Med Interne 1993; 14: 194
71. Slavich IL, Gleffe RF, Haas EJ. Grand mal epileptic seizures during ciprofloxacin therapy. JAMA 1989; 261: 558-9
72. Karki SD, Bentley DW, Raghavan M. Seizure with ciprofloxacin and theophylline combined therapy. DICP 1990; 24 (6): 595-6
73. Semel JD, Allen N. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. South Med J 1991; 84: 465-8
74. Abouesh A, Stone C, Hobbs WR. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. J Clin Psychopharmacol 2002; 22: 71-81
75. Lucet JC, Tilly J, Lerebours G, et al. Neurological toxicity related to pefloxacin [letter]. J Antimicrob Chemother 1988; 21: 811-2
76. Walton GD, Hon JK, Mulpur TG. Ofloxacin-induced seizures. Ann Pharmacother 1997; 31 (12): 1475-7
77. Jeandel C, Laurain MC, Jouanny P, et al. État de mal épileptique sous ofloxacine. Rev Med Interne 1994; 15: 218-9
78. Leone R, Venegoni M, Motola D, et al. Adverse drug reactions related to the use of fluoroquinolone anti-

microbials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. Drug Saf 2003; 26 (2): 109-20

79. Halliwell RF, Su J, Demuro A, et al. Characterization of the interaction between a novel convulsant agent, norbiphen, and GABAA and other ligand-gated ion channels. Neuropharmacology 2002; 43: 778-87
80. Shimada J, Hori S. Adverse effects of fluoroquinolones. Prog Drug Res 1992; 38: 133-43
81. Kim J, Ohtani H, Tsujimoto M, et al. Quantitative comparison of the convulsive activity of combinations of twelve fluoroquinolones with five nonsteroidal anti-inflammatory agents. Drug Metab Pharmacokinet 2009; 24 (2): 167-74
82. Marinella MA. Myoclonus and generalized seizures associated with gatifloxacin treatment. Arch Intern Med 2001; 161: 2261-2
83. Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. Drugs Aging 2003; 20 (4): 289-302
84. Lahmek P, Michel L, Meunier N, et al. A seizure attributed to ofloxacine in a woman undergoing detoxification for alcohol dependence. Case Report Med. Epub 2010 Jan 24
85. Agbaht K, Bitik B, Piskinpasa S, et al. Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. Int J Clin Pharmacol Ther 2009; 47 (5): 303-10
86. Hall CE, Keegan H, Rogstad KE. Psychiatric side effects of ofloxacin used in the treatment of pelvic inflammatory disease. Int J STD AIDS 2003; 14 (9): 636-7
87. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. Am J Med 1991; 90 (4): 528-9
88. Grimm O, Alm B, Fur Seelische Z. A case of ciprofloxacin-induced acute polymorphic psychosis with a distinct deficit in executive functions [letter]. Psychosomatics 2007; 48 (3): 269
89. Norra C, Skobel E, Breuer C, et al. Ciprofloxacin-induced acute psychosis in a patient with multidrug-resistant tuberculosis. Eur Psychiatry 2003; 18 (5): 262-3
90. Farrington J, Stoudemire A, Tierney J. The role of ciprofloxacin in a patient with delirium due to multiple etiologies. Gen Hosp Psychiatry 1995; 17: 47-53
91. Fennig S, Mauas L. Ofloxacin-induced delirium [letter]. J Clin Psychiatry 1992; 53 (4): 137-8
92. Ahuja N, Lloyd AJ. Antibiomania and ciprofloxacin-induced mania [letter]. Psychosomatics 2007; 48 (4): 36
93. de Bazignan AD, Thiessard F, Miremont-Salamé G, et al. Psychiatric adverse effects of fluoroquinolones: review of cases from the French pharmacologic surveillance database. Rev Med Interne 2006; 27 (6): 448-52
94. Steinert T, Studemund H. Acute delusional parasitosis under treatment with ciprofloxacin. Pharmacopsychiatry 2006; 39 (4): 159-60
95. Cheung YF, Wong WW, Tang KW, et al. Ciprofloxacin-induced palatal tremor. Mov Disord 2007; 22 (7): 1038-43
96. Lee CH, Cheung RTF, Chan TM. Ciprofloxacin-induced oral facial dyskinesia in a patient with normal liver and renal function. Hosp Med 2000; 61: 142-3
97. Azar S, Ramjiani A, Van Gerpen JA. Ciprofloxacin-induced chorea. Mov Disord 2005; 20: 513-4
98. Pastor P, Moitinho E, Elizalde I, et al. Reversible oral-facial dyskinesia in a patient receiving ciprofloxacin hydrochloride. J Neurol 1996; 243: 616-7
99. MacLeod W. Case report: severe neurological reaction to ciprofloxacin. Can Fam Physician 2001; 47: 553-5
100. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. Ann Pharmacother 1996; 30: 138-41
101. Post B, Koelman JHTM, Tijssen MAJ. Propriospinal myoclonus after treatment with ciprofloxacin. Mov Disord 2004; 19: 595-7
102. Mohan N, Menon K, Rao PG. Oral gatifloxacin-induced ataxia [letter]. Am J Health Syst Pharm 2002; 59 (19): 1894
103. Rosolen A, Drigo P, Zanesco L. Acute hemiparesis associated with ciprofloxacin [letter]. BMJ 1994; 309: 1411
104. Upton C. Sleep disturbance in children treated with ofloxacin [letter]. BMJ 1994; 309: 141
105. Akhtar S, Ahmad H. Ciprofloxacin-induced catatonia [letter]. J Clin Psychiatry 1993; 54: 115-6
106. Youssef NA, Benazzi F, Desan PH. Levofloxacin-induced catatonia. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33 (4): 741-2
107. Rauser EH, Ariano ER, Anderson AD. Exacerbation of myasthenia gravis by norfloxacin. DCIP Ann Pharmacother 1990; 240: 207-8
108. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis [letter]. BMJ 1990; 301: 818
109. Fraser AG, Harrower ADB. Convulsions and hyperglycaemia associated with nalidixic acid [letter]. BMJ 1977; 2 (6101): 1578
110. Striano P, Zara F, Coppola A, et al. Epileptic myoclonus as ciprofloxacin-associated adverse effect. Mov Disord 2007; 22 (11): 1675-6
111. Bellon A, Perez-Garcia G, Coverdale JH, et al. Seizures associated with levofloxacin: case presentation and literature review. Eur J Clin Pharmacol 2009; 65 (10): 959-62
112. Kisa C, Yildirim SG, Aydemir C, et al. Prolonged electroconvulsive therapy seizure in a patient taking ciprofloxacin. J ECT 2005; 21 (1): 43-4
113. LaSalvia EA, Domek GJ, Gitlin DF. Fluoroquinolone-induced suicidal ideation. Gen Hosp Psychiatry 2010 Jan-Feb; 32 (1): 108-10
114. Sire S, Staub-Schmidt T, Ragnaud JM, et al. À prpos d'une crise comitiale sous ofloxacine. Rev Med Interne 1996; 17: 601-2
115. Barrett MJ, Login IS. Gemifloxacin-associated neurotoxicity presenting as encephalopathy. Ann Pharmacother 2009; 43 (4): 782-4
116. Heyd A, Haverstock D. Retrospective analysis of the safety profile of oral and intravenous ciprofloxacin in a geriatric population. Clin Ther 2000; 22 (10): 1239-50
117. Bertino Jr J, Fish D. The safety profile of the fluoroquinolones. Clin Ther 2000; 22 (7): 798-817
118. Stahlmann R, Lode H. Toxicity of quinolones. Drugs 1999; 58 Suppl. 2: 37-42
119. Cipro®: summary of product characteristics. Wayne (NJ): Bayer Healthcare Pharmaceuticals Inc., 2009
120. Tavanic® 500 mg tablets: summary of product characteristics. Guildford: Sanofi-Aventis, 2009

121. Seizure: causes [online]. Available from URL: http://en.wikipedia.org/wiki/Seizure#Causes [Accessed 2010 Feb 15]
122. Akaike N, Shirasaki T, Yakushiji T. Quinolone and fenbufen interact with GABA(A) receptor in dissociated hippocampal cells of rat. J Neuropsychol 1991; 66 (2): 497-504
123. Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. Br J Clin Pharmacol 1996; 41 (4): 277-84
124. Sweweb [online]. Available from: URL: http://sweweb.mpa.se/swedisii/ [Accessed 2010 Feb 15]
125. Utinor® tablets 400 mg: summary of product characteristics. Whitehouse Station (NJ): Merck Sharp & Dohme Limited, 2009
126. Tarivid® 200 mg and 400 mg tablets: summary of product characteristics. Guildford: Sanofi-Aventis, 2009
127. US FDA. Risk of fluoroquinolone-associated myasthenia gravis exacerbation February 2011 label changes for fluoroquinolones [online]. Available from URL: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm247115.htm2011 [Accessed 2011 Apr 18]

Correspondence: Dr *Ana Maria Tomé*, Medical Department, Grupo Tecnimede, Zona Industrial da Abrunheira, Rua da Tapada Grande, n.° 2 – Abrunheira, 2710-089 Sintra, Portugal.
E-mail: dmed.fv@tecnimede.pt