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Quinolone-induced psychosis: an updated review

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Quinolones are an antibiotic group widely used due to their antimicrobial action and security profile, however, it has been described neuropsychiatric adverse effects, being induced-psychotic episodes one of the most clinically relevant. Nevertheless, this secondary effect has been scarcely studied. A literature search using PRISMA guidelines was performed between 01/01/1962 and 01/31/2019 on PubMed and ScienceDirect, including manuscripts which described substance-induced psychotic disorder according to DSM-5 and in which the symptomatology was not attributable to an acute confusional state (delirium) or to other induced psychiatric disorders. 459 articles were found, but only 27 manuscripts fulfilled inclusion criteria (n=27 patients, median age of 36.15±16.96 years). Ciprofloxacin, levofloxacin and ofloxacin were the main antibiotics implicated. Quinolone-induced psychosis is a clinical relevant issue due to the high prescription of these antibiotics and the severity of this clinical syndrome. In general, this syndrome can remit in a few days with the withdrawal of the quinolone and performing symptomatic support if it is necessary. Finally, it is important to perform further research on this issue.

Keywords: Quinolones, Psychosis, Ciprofloxacin, Levofloxacinn, Psychotic Induced Disorder

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Psicosis inducidas por quinolonas: una revisión actualizada

Las quinolonas son un grupo de antibióticos ampliamente usado por su perfil antibacteriano y de seguridad. Sin embargo, se han descrito algunos efectos secundarios neuropsiquiátricos, entre ellos episodios psicóticos asociados a su uso. Este efecto adverso ha sido poco estudiado, a pesar de su relevancia clínica. Por ello, realizamos una revisión de la literatura usando la guía PRISMA, la búsqueda se realizó en PubMed y ScienceDirect incluyendo manuscritos entre el 01/01/1962 hasta el 31/01/2019 donde se describieran trastorno psicótico inducido por medicamentos/sustancias según el DSM-5, y que además la sintomatología psicótica fuese principalmente atribuible a una quinolona, que los pacientes no tuvieran antecedentes de trastorno psiquiátrico primario que curse con psicosis, y que la sintomatología predominante no fuese atribuible a un estado confusional agudo (delirium) ni a otros trastornos psiquiátricos inducidos. Se detectaron 459 artículos de los que 27 publicaciones cumplían los criterios de inclusión y exclusión (n=27 pacientes, edad media 36,15±16,96). Las tres quinolonas más frecuentemente relacionadas con episodios psicóticos fueron: ciprofloxacino, levofloxacino y ofloxacino. Las vías de administración más comunes eran la oral e intravenosa. Se puede concluir que clínicamente es importante tener en cuenta este efecto adverso dada la alta frecuencia de prescripción de estos fármacos y la gravedad que implica la presencia de síntomas psicóticos. En general, este cuadro puede remitir rápidamente en pocos días con el retiro de la quinolona y realizando un soporte sintomático si es necesario. Finalmente, es importante realizar más investigaciones en esta área.

Palabras clave: Quinolonas, Psicosis, Ciprofloxacina, Levofloxacina, Trastorno Psicótico Inducido

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INTRODUCTION

Quinolones are a widely used antibiotic groups since the 60s due to the antibacterial and safety profile[1-3]. Classically, quinolones have been divided into four generations according to the evolution in their pharmacokinetics related to changes in their molecular structure[2-4], with the particularity that from the second generation all molecules are fluorinated, which is why they are called fluoroquinolones from the second to the fourth generation[2,3]. Regardless of their differences, all quinolones act through binding with several vital enzymes for the replication, transcription, and repair of bacterial deoxyribonucleic acid (DNA). Of these enzymes, the most important are DNA gyrase and topoisomerases II and IV[3]. The antibacterial spectrum of quinolones increases with each generation, being fourth-generation fluoroquinolones that cover the widest spectrum, including gram-negative, gram-positive, anaerobic, and even mycobacteria[1-3,5]. Hence, the therapeutic indications are broad and include infections in several organs and systems (e.g. skin, urinary tract, gastrointestinal and respiratory systems, among others)[2,3].

The molecular structure of quinolones confers their antibacterial activity, but also their side effects[4]. Although quinolones are commonly described as being well tolerated[1], the adverse event rate is 9.2 per 10,000 prescriptions[6]. Adverse or secondary effects related to the central nervous system (CNS) are considered to be the second most frequent after the gastrointestinal adverse effects[1,4,7], although some authors point out that there may be an overrepresentation of CNS adverse events given the characteristics of the clinical symptoms and the system involved[7]. In any event, it is estimated that between 1 and 4.4% of patients on quinolone treatment will have some neuropsychiatric adverse effect, and only 0.5% will be a critical event[7]. Within the wide range of neuropsychiatric effects are described: delirium and other confusional states, mania, psychosis, insomnia, among others[7]. Although there is no consensus on the frequency of quinolone-induced psychosis, there could be an overdiagnosis bias given the severity of this event, its possible confusion with delirium, and that it is relatively easy to identify[7]. On the other hand, it is important to highlight that not only quinolones have been associated with the induction of psychosis, but also other groups of antibiotics such as penicillins and trimethoprim-sulfamethoxazole[8].

Neuropsychiatric effects, including induced psychoses, are postulated to be related to substituents that bind at position 7 of the quinolone structure[1,4]. Molecules in this position have a certain affinity for the gamma-aminobutyric acid (GABA) receptor, so it would displace GABA from its receptor[1,4]. Furthermore, interactions with the N-methyl-D-aspartate receptor (NDMA) have been described that could explain some of the neuropsychiatric effects[9]. Although there are some fluoroquinolones that have a higher blood-brain barrier passage, it does not appear that this may be related to the ability to induce neuropsychiatric effects[1]. In a specific review on this issue, ciprofloxacin and ofloxacin have been described as the most frequently related to neuropsychiatric events[7].

Despite the report of several cases of psychosis induced by different fluoroquinolones (see Tomé and Filipe, 2011[7]), in the few reviews of this association, it is usually confused or considered confusional syndromes (delirium) and psychotic spectrum disorders as the same diagnosis[7,10]. Therefore, more studies are needed to discern this relationship and given the high frequency of prescription of this pharmacological group, we propose a review of the literature on quinolone-induced psychosis.

METHODS

Search strategy

A review of the literature was conducted according to the PRISMA guidelines on the PubMed and ScienceDirect platforms from 01/01/1962 to 01/31/2019. The terms included in the search were as follows: Quinolones AND induced psychosis; Ciprofloxacin AND induced psychosis; fleroxacin AND induced psychosis; Moxifloxacin AND induced psychosis; Norfloxacin AND induced psychosis; Gatifloxacin AND induced psychosis; Levofloxacin AND induced psychosis; Ofloxacin AND induced psychosis; Trovafloxacin AND induced psychosis; Gemifloxacin AND induced psychosis; Grepafloxacin AND induced psychosis; Sparfloxacin AND induced psychosis; Lomefloxacin AND induced psychosis; Difloxacin AND induced psychosis; Tosufloxacin AND induced psychosis; Plefloxacin AND induced psychosis; Quinolones AND psychiatric symptoms; levofloxacin AND hallucinations; Gatifloxacin AND Hallucinations; quinolones AND induced delusions; Nalidixic acid AND induced psychosis; Oxolinic Acid AND Induced Psychosis.

Inclusion and exclusion criteria

Articles published in Spanish or English were included in which psychotic symptoms were predominantly and clearly described (meeting criteria of Psychotic Disorder induced by drugs/substances according to DSM-5[13]), and those in which the psychotic symptoms were mainly attributable to a quinolone and not another concomitant medication. Patients who had history of a primary psychotic disorder (schizophrenia, schizoaffective disorder, bipolar disorder) were excluded. Also, cases that reported symptoms attributable to an acute confusional state (delirium) or to any other

induced psychiatric disorders such as a manic episode or a depressive disorder with psychotic symptoms were excluded.

Data extraction and analysis

The following data were extracted: type of study and n of each report, sex, age, quinolone prescribed, dose, route of administration, the indication for prescription, concomitant treatment, time of onset of psychotic symptoms, psychotic symptoms (description of symptoms), type of management for treating psychotic symptoms, presence of Naranjo criteria[14] or not.

RESULTS

485 potential articles were detected in the initial search. After reading the title and abstract, 136 articles were selected for a complete reading. Three articles not included in the initial search were found by manually reviewing the references. Finally, only 27 publications fulfilled the inclusion and exclusion criteria after the complete reading of the manuscript (see figure 1). These 27 publications included 27 patients who fulfilled the criteria of the current review. The vast majority of the articles included are case reports and not all of them specified Naranjo criteria or other specific criteria for causality. The findings will be described in the following sections and the included cases are summarized in table 1.

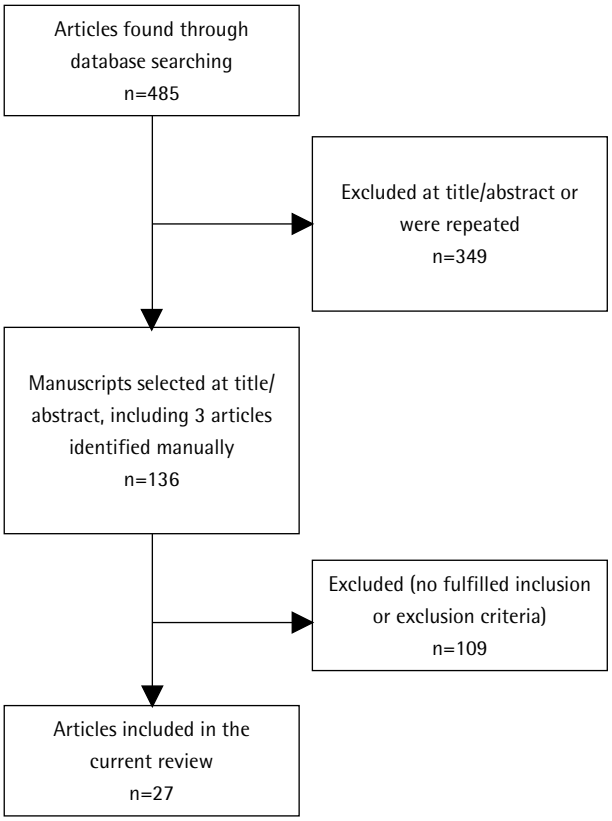

Figure 1 | *Flow chart*

Note that some studies with large samples clearly reported the presence of psychotic symptoms in certain groups (e.g. older population), however, they also included delirium with psychotic symptoms within the same group, hence, they were not included in the current review (see Sellick et al., 2018[10]).

Age and sex

Of the 27 patients described in the reports, 17 were women and 10 were men. The mean age was 36.15±16.96 years, covering cases from 4 to 67 years. Only 1 case did not report the age. Note the finding of 2 case reports in minors, specifically 2 girls aged 4 and 6 years old, both cases being treated with ofloxacin for gastroenteritis[15,16].

Antibiotic

In relation to antibiotics, the quinolones found in this review were: ciprofloxacin (13 cases), levofloxacin (5 patients), and ofloxacin (4 cases), moxifloxacin (2 patients), and finally perfloxacin, norfloxacin, and gatifloxacin with a case each. The infections for which quinolone treatments were prescribed are diverse and involve most of the organ systems systems. The most frequent cause of treatment was urinary tract infection (UTI) for a total of 7 cases[17-22]. Gastrointestional tract infections were the second in frequency, with 7 case[15,16,23-27]. Another frequent cause of quinolone treatment is lower respiratory tract infections, in total 7 cases among different infections (pneumonia, tuberculosis, etc.)[28-33].

Other infectious etiologies included to be highlighted are infections of the male reproductive system with two cases[34,35] and female with one case[36], upper respiratory infection[37], dermatological infection with one case,[38] and one case of bacterial conjunctivitis treated with ciprofloxacin eye drops.[39]

Administration route and doses

Regarding the doses administered and the routes of administration used, we found that the route of administra-

Table 1 Summary of cases

Authors and year of publication	Type of study	n	Sex/age (years)	Doses	Administration route	Indication	Onset of psychotic symptoms	Naranjo criteria	Concomitant medication	Commentaries	Treatment	Resolution of the psychotic disorder
Ciprofloxacin												
Rossi & Mazoki, 2018[34]	Case report	1	Man/36	500mg/day	Oral	Epididymitis	ND	No	ND	The patient reached cannabis abstinence two weeks before the antibiotic was prescribed (cannabis use disorder since 17 years old).	Withdrawal of medication	5 days
Ranjan & Praharaj, 2014[23]	Case report	1	Woman/22	IV: 300mg/day during 3 days Oral: 750mg/day during 3 days	IV and oral	Gastroenteritis	ND	6	No	Auditive and visual, hallucinations, fears, and psychomotor slowdown. No family or personal psychiatric history.	Withdrawal of medication	2-3 days
Ben-Chetrit et al. 2013[31]	Case report	1	Man/64	ND	ND	Chronic obstructive pulmonary disease with infected bronchiectasis	4th day	No	Cefuroxime, ramipril, ipratropium bromide inhaler	He had some confusional symptoms at the onset of psychotic symptoms. Visual hallucinations were prominent.	Withdrawal of medication	24 hours
Grimm et al., 2007[17]	Case report	1	Womenr/45	500mg/day	Oral	Urinary tract infection	7th day	No	No	Reference and persecutory delusions with formal thought disorder. Auditory hallucinations. Emotional lability and tendency to aggressiveness. There was a suspicion of schizoaffective disorder.	Aripiprazole 15mg/day	Day 9
Steinert & Studemund, 2006[18]	Case report	1	Men/45	200mg/day	Oral	Urinary tract infection	1st day	No	No	Visual hallucinations and delusional infestation (with skin self-harm). No cognitive impairments. No psychiatric history.	Withdrawal of medication	Day 2

Table 1 Continuation

Authors and year of publication	Type of study	n	Sex/age (years)	Doses	Administration route	Indication	Onset of psychotic symptoms	Naranjo criteria	Concomitant medication	Commentaries	Treatment	Resolution of the psychotic disorder
Norra et al., 2003[33]	Case report	1	Women/32	250mg/day	Oral	Tuberculosis	2nd day	No	Isoniazid, ethambutol, pyrazinamide, rifampicin	Visual and auditives hallucinations, anxiety. She had confusional symptoms at the onset. One brother with schizophrenia.	Withdrawal of medication	Day 2
Tripathi et al. 2002[39]	Case report	1	Women/27	ND	Topic (eye drops)	Bacterial conjunctivitis	2 hours	No	No	Visual and auditive hallucinations, disorganization of speech and behavioral disturbances. No medical, toxicological or psychiatric history.	Withdrawal of medication	12 hours
James & Demian, 1998[24]	Case report	1	Man/31	800mg/day	IV	Intestinal sepsis	15th day	No	Piperacillin, Metronidazole, Gentamicin, Fluconazole	Delusions, visual hallucinations and behavioral disturbances. No psychiatric history.	Withdrawal of medication	Day 9
Zabala et al., 1998[25]	Case report	1	Man/58	400mg/day	IV	Bacterial diarrhea	1st day	No	Baclofene	Patient with transverse myelitis, neurogenic bladder and frequent episodes of urinary infection.	Withdrawal of medication	36 hours
Mulhall & Bergmann, 1995[19]	Case report	1	Woman/62	IV: 800mg/day during one day. Oral: 1000mg/day	IV and oral	Urinary tract infection	3rd day	No	No	Delusions, hallucinations and agitation. No psychiatric history.	Withdrawal of medication, haloperidol was prescribed for agitation (5mg single doses)	24 hours
Reeves, 1992[35]	Case report	1	Man/49	500mg/day	Oral	Prostatitis	2nd day	No	No	The patient had some paranoic traits but did not fulfilled criteria for any disorder.	Thiotixen 25mg/day	Day 3
Meher et al., 1992[26]	Case report	1	Woman/35	1500mg/day	Oral	*Salmonella typhi* sepsis	7th day	No	No	Visual habllucinations and violent behavior. No psychiatric history.	Withdrawal of medication, diazepam 10mg single doses	Day 3

Table 1 Continuation

Authors and year of publication	Type of study	n	Sex/age (years)	Doses	Administration route	Indication	Onset of psychotic symptoms	Naranjo criteria	Concomitant medication	Commentaries	Treatment	Resolution of the psychotic disorder
McCue & Zandt, 1991[20]	Case report	2 (only 1 case fulfilled criteria)	Woman/27	750mg/day	Oral	Urinary tract infection	5th day	No	Trimethoprim-sulfamethoxazole, zidovudine	Patient with human immunodeficiency virus. He was in methadone maintenance program for substance use disorder.	Withdrawal of medication. Haloperidol was used depending on symptoms	Day 5
Moxifloxacin												
Higdon et al., 2017[28]	Case report	1	Woman/24	400mg/day	IV	Sepsis secondary to pneumococcal pneumonia	3rd day	No	Vancomycin, piperacillin/ tazobactam, ceftriaxone, hydroxychloroquine, prednisone	The patient had lupus erythematosus with corticosteroid management.	Withdrawal of medication	Day 1
Mazhar et al., 2016[40]	Case report	1	Man/40	400mg/day	Oral	Bronchitis	3rd day	5	Acetaminophen	Visual and auditive hallucinations, anxiety. No personal or family psychiatric history.	Withdrawal of medication	20 hours
Ofloxacin												
Chauhan et al., 2013[15]	Case report	1	Woman/5	100mg/day	Oral	Gastroenteritis	1st day	No	Lamotrigine, valproate, metronidazole and ondasetron	Epilepsy history in treatment with lamotrigine and valproate. She received ornidazol, ondansetron and ofloxaxine at the same time. Complete remission after 1 day of sedation.	Sedation (it is not specified what type of sedation)	24 hours
Koul et al., 2009[21]	Case report	1	Woman/18	800mg/day	Oral	Urinary tract infection	2nd day	No	Metronidazole	psychomotor slowdown and agitation, persecutory and reference delusions, auditive hallucinations, anxiety and emotional lability.	Risperidone 2mg/day and citalopram 20mg/day	Day 4
Bhattacharya et al., 2017[16]	Case report	1	Woman/4	1600mg/ day	IV y oral	Gastroenteritis	3rd day	3	Ondansetron	Visual and tactil hallucinations after ofloxacin overdose.	Olanzapine 2,5mg	Day 3

Table 1 Continuation

Authors and year of publication	Type of study	n	Sex/age (years)	Doses	Administration route	Indication	Onset of psychotic symptoms	Naranjo criteria	Concomitant medication	Commentaries	Treatment	Resolution of the psychotic disorder
Hall et al., 2003[36]	Case report	2 (only 1 case fulfilled criteria))	Women/32	800mg/12day	ND	Pelvic inflammatory disease	1st day	3	ND	Nihilistic delusions, psychotic anxiety. She had one episode of depression and panic disorder that was successfully treated with fluoxetine 1 year before the ofloxacin treatment.	Withdrawal of medication	Day 2
Gatifloxacin												
Adams & Tavakoli, 2006[29]	Case report	1	Man/19	400mg/day	Oral	Community-acquired pneumonia	1st day	3	Acetaminophen, at the 3rd day piperacilin/ tazobactam was prescrtibed	Paranoid delusions and visual hallucinations in the first day after gatifloxacin onset. He had one brother with bipolar disorder.	Withdrawal of medication	24 hours
Levofloxacin												
Steuber et al., 2018[30]	Case report	1	Woman/67	750mg/day	Oral	Community-acquired pneumonia	3rd day	5	Azithromycin, ambrisentan, calcium citrate, fexofenadine, tramadol, cevimeline, tadalafil	Rheumatologic history with one episode of psychosis induced by steroids. Brain atrophy vs. hydrocephalus without changes in the last 3 years.	Withdrawal of medication, lorazepam 0.5mg and aripiprazol 2,5mg.	Day 3
Kiangkitiwan et al., 2008[37]	Case report	1	Woman/42	500mg/day	Oral	Sinusitis and urinary tract infection	4th day	3	Meclizine and guaifenesin/ phenylpropanolamine	The first symptoms were nonspecific and began on the 2nd day after levofloxacin was started. Psychotic symptoms appeared on the 4th day. Second-degree relative with bipolar disorder.	Withdrawal of medication	24 hours

Table 1 Continuation

Authors and year of publication	Type of study	n	Sex/age (years)	Doses	Administration route	Indication	Onset of psychotic symptoms	Naranjo criteria	Concomitant medication	Commentaries	Treatment	Resolution of the psychotic disorder
Takser & Grad, 2017[41]	Case report	1	Woman/22	500mg single dosis	Oral	Urinary tract infection	3 hours	No	No	Visual hallucinations, derealization feeling, insomnia and nightmares. No personal psychiatric history, one first-degree relative had cocaine use disorder.	Withdrawal of medication	Day 3
Moorthy et al., 200838	Case report	1	Men/50	500mg/day	Oral	Cellulitis	1st day	3	Amoxicillin/ clavulanate the previous 10 days	The patient was using amoxiciline/ clavulanate the previous 10 days. The first day that patient used levofloxacin presented psychotic symptoms.	Withdrawal of medication	Day 2
Agu et al., 2015	Case report	1	Men/25	ND	IV	Complicated pneumonia	1st day	No	Vancomycin, meropenem	The psychotic symptoms only appeared after intrevnous lefloxacine was prescribed.	Withdrawal of medication	ND
Norfloxacin												
Jain et al., 1994[27]	Case report	1	Woman/nd	800mg/day	IV	Bacillary dysentery	2nd day	No	No	No psychiatric history.	Withdrawal of medication, chlorpromazine and diazepam	Day 3
Plefloxacin												
Hesslinger et al., 1996[22]	Case report	1	Woman/59	800mg/day	Oral	Urinary tract infection	1st day	No	Acetaminophen	The patient had history of one maniac episode induced by steroids. He presented some hypomanic symptoms.	Perazine 500mg/day	Day 9

* After antibiotic was started

IV: intravenous; ND: No data

tion most frequently used was oral (19 of the 27 cases) [15-23,29,30,33-38,40,41]. Intravenous administration was the second in frequency with 8 of the 27 patients[16,19,23-25.27,28,32]. In 3 of these 8 cases, a transition to oral administration was performed after using the intravenous route initially[16,19,23]. A case that should be mentioned is the case of a 25-year-old male patient who received intravenous treatment with levofloxacin for a complicated pneumonia, presenting only psychotic symptoms with intravenous treatment[32]. The topical route was reported on one occasion (ophthalmic use); note that in this case, the psychotic symptoms appeared after the administration of the third dose of the antibiotic in the form of eye drops, and that they remitted 12 hours after their withdrawal[39]. Regarding the doses, in general, all cases received usual doses of each drug, although one case presented psychotic symptoms with an overdose of ofloxacin use[16]. In this case, an intravenous dose of 70 mg/day calculated by the weight of the patient was initially administered, and then a dose of 100mg/12 hours was prescribed orally, but by mistake 400mg/12 hours was administered. After administration of the first wrong oral dose, psychotic symptoms started[16]. No publications were found that reported other routes of administration.

Concomitant medication

Concomitant administration of other antibiotics was documented in 11 of the 27 cases included[15,2021,24,28-33,36,38]. Metronidazole was the most frequent concomitant medication used[15,21,24,36]. Other medications simultaneously prescribed with some frequency were acetaminophen[22,29,40] and ondansetron[15,16]. Only in 3 cases did not report whether another treatment was being administered concomitantly[26,34].

Clinical features and treatment

Regarding the symptomatology described, the most frequently reported psychotic symptoms were visual hallucinations, delusions, and behavioral alterations. These symptoms appeared simultaneously, and without other accompanying major psychopathological symptoms, in most of the reported cases[16-19,21-24,26-29,31-36,39-41]. Although three cases described symptoms suggestive of an acute confusional state[15,25,37], those cases were included in the review because those symptoms were brief (few hours), and also, beacuse they may be related to formal thought disturbances. Additionally, assessing the evolution of each case, psychotic symptoms were predominants.

The time of onset of psychotic symptoms after the initiation of quinolone treatment among the cases included in our review was highly variable (between hours and days). Only 2 cases exceeded 8 days after the administration of the first dose[17,24]. In most cases, psychiatric symptoms remitted within the first 72 hours after quinolone withdrawal. In 8 cases, the psychotic symptoms resolved in the first 24 hours after the withdrawal of the drug[15,19,28,29,31,37,39,40].

Analyzing the measures taken to control psychotic symptoms in all the cases described, quinolone was withdrawn as part of therapeutic management. In 15 cases, withdrawal of quinolone was the main measure taken[18,23,25,28,29,31-34,36,38-41]. In some cases, the use of antipsychotics was necessary concomitantly with the withdrawal of quinolone. The most frequently used antipsychotics were haloperidol and aripiprazole, with two cases of each[17,19,20,30]. Other antipsychotics used were: olanzapine, risperidone, thiothixene, chlorpromazine, and perazine, which were used in 1 case each[16,19,21,22,27]. Other psychotropic drugs used were diazepam[26,27] and lorazepam[30].

Among the cases included, only three had previously presented psychiatric symptoms, which had completely remitted by the time the antibiotic treatment with quinolones was started[22,30,36]. One case was a 32-year-old female who had presented a major depressive episode a year before treatment with ofloxacin. She received fluoxetine treatment and the depressive symptoms remitted completely[36]. Two other case reports describe a case with a history of having suffered a psychotic episode related to the use of steroids for the treatment of lupus erythematosus[30], and in another case a steroid-induced manic episode[22]; both cases had completely remitted before the time the patients received quinolone treatment. On the other hand, there are two cases that reported the use of toxic substances: in the first case, a 36-year-old man who received treatment with ciprofloxacin for epididymitis, had been using cannabis in a pattern of dependency since the age of 17 and the last consumption had been 2 weeks before the start of the antibiotic prescription[34]. The other case was a patient with a history of human immunodeficiency virus and intravenous drug use[20].

Regarding family history, a case was reported of a patient with a brother with schizophrenia[33] and, finally, two other reports, two other reports describe a family history of bipolar disorder[29,37].

Importantly, in some cases, there was suspicion that the quinolone-induced psychotic episode could be a first episode of a primary psychotic disorder. Thus, Grimm et al. (2007)[17] describe that the reported case of a ciprofloxacin-induced psychotic episode could be part of a schizoaffective disorder, and therefore, it was important to observe its evolution.

DISCUSSION

Despite the frequency with which fluoroquinolone-induced psychosis appears to be described in the literature, there are few articles found that specifically correspond to this diagnostic entity (quinolone-induced psychotic disorder) and do not consider other diagnoses that may frequently be confused with psychotic spectrum disorders (e.g. delirium). Of the three quinolones most frequently found in this review (ciprofloxacin, levofloxacin, ofloxacin), it should be mentioned that, although it might suggest that they have a somewhat greater capacity to generate psychosis, it is more likely to be related to the frequency of prescription of these quinolones, especially ciprofloxacin and levofloxacin[7,10]. Note that ciprofloxacin is frequently described in reviews of CNS adverse effects. For example, Sellick et al. (2017) indicate prevalences of up to 3.6% of delirium/psychosis in older patients treated with this quinolone[10]. Ofloxacin has a high frequency of reports of CNS adverse effects, which is why some authors highlight that it may be overrepresented given the low prescription rate and great alarm regarding the adverse effects of this quinolone[7]. Levofloxacin (L-isomer of ofloxacin) is described as safer and with little or no psychosis rates (1 in a million prescriptions),[1,10,42] however, in this review, it appears to be the third quinolone involved. This may be due to the high frequency of their prescription[10].

Regarding the administration routes, most of the reported cases indicate the oral and intravenous routes, which is to be expected given that they are the most widely used administration routes[5]. The intravenous route is generally preferred in severe infections due to the high bioavailability of the treatment[43], and due to the same higher bioavailability, the adverse effects would be expected to be more frequent. However, in the case of ciprofloxacin, there do not appear to be differences in terms of adverse effects between these two routes[44], although we highlight the case reported by Agu et al. (2015) where they point out that the patient presented psychotic symptoms with the intravenous use of ciprofloxacin and not with the oral administration.[32] Finally, it is important to highlight the case of psychosis induced by ophthalmic ciprofloxacin[39]. This case is interesting given that the use of quinolones by topical/ophthalmic route is usually in low doses; even so, it is known that some quinolones are absorbed ophthalmically[45]. Therefore, this case could imply that even low doses of ciprofloxacin could generate psychotic symptoms.

Urinary tract infection was the most frequent cause found in our cases for which quinolones were prescribed. The presence of urinary infection in patients with psychosis seems to be frequent, reaching a prevalence of up to 21%[46-48]. It is important to keep in mind that many of the mechanisms by which a urinary infection (or any other infections) can generate or precipitate neuropsychiatric symptoms are unknown, being a mixture of mechanisms, and where inflammatory factors could have a crucial relevance[47]. The second most frequent infection was gastrointestinal tract infections. There is currently a great interest in the gastrointestinal microbiota and mental disorders[49], being described a great potential in this area of research to better understand disorders such as schizophrenia[49]. If we consider that antibiotics, in general, alter the gastrointestinal microbiota[50], we could suppose that this alteration of the microbiota may at least partly explain some of the symptoms described in the current review.

In general, the onset of psychotic symptoms occurred in the first days of the start of any of the quinolones prescribed, being an important criterion for causality. The withdrawal of quinolone was the most important measure for the treatment of induced psychotic symptoms, although in some cases antipsychotics or benzodiazepines were prescribed (as *off label*). Remission of the clinical disorder was rapid in general, with few cases having symptoms beyond the fifth day and only two cases having remission beyond the eighth day.

It is important to point out that in some of the cases described there was suspicion that could be a first psychotic episode of primary psychosis (although quinolone had precipitated psychosis), so follow-up should be necessary to be able to do a more accurate diagnosis[17]. Although having a diagnosis of primary psychotic disorder was an exclusion criterion for the present review, several of the patients had a relevant psychiatric history. For example, the use of substances is a risk factor for psychosis[51]. However, it is important to highlight that some of the cases indicate that there was an abstinence period when they presented psychotic symptoms[34]. Another case had a family history of schizophrenia, another risk factor for psychotic disorders[33,52].

On the other hand, several cases had concomitantly other medications prescribed, although it should be noted that quinolone was the final medication that precipitated psychotic symptoms. In this line, several groups of antibiotics have been associated with psychotic symptoms[8,53]. Other medications such as acetaminophen and ondansetron were frequently prescribed. Acetaminophen has been very rarely associated with cases of psychosis[54], while ondansetron has been studied as an adjunctive treatment in psychotic disorders[55,56].

This review has several limitations such no all cases reported causality criteria (e.g. Naranjo criteria[14]). In some cases, there is also use of other medications that could be associated with psychotic symptoms. Finally, it is possible that in the description of each case there are symptoms that were not fully mentioned, and hence, there could be some bias

due to the possibility of being similar symptoms classified simply as "psychosis" (e.g. affective syndromes with psychotic symptoms or delirium). On the other hand, the current review is exhaustive and tries to cover in a systematic way the cases in which quinolones have induced frank psychotic symptoms and that fulfilled criteria of induced psychotic disorders.

Quinolones have various neuropsychiatric effects, with psychosis being one of them. Although, there would not seem to exist a specific pattern, in the current review there are some infections (e.g. urinary tract infections) and quinolones more frequently implicated (e.g. ciprofloxacin, levofloxacin), as well as the possibility of the presence of certain predisposing family and personal history. Although the exact mechanism is not entirely known, clinically it is important to take into account this adverse effect given the high frequency of prescription of these medications and the severity of the presence of psychotic symptoms. Finally, it is important to perform further research in this area.

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