

Infectious Diseases

Peripheral Neuropathy Associated with Fluoroquinolones

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OBJECTIVE: To survey cases of fluoroquinolone-associated adverse events that included peripheral nervous system (PNS) symptoms posted on Internet Web sites.

METHODS: Cases were obtained with the assistance of members of Web sites formed by people sustaining fluoroquinolone-related events. Information obtained met the standards of MedWatch, and each reported case was assessed using the Naranjo probability scale.

RESULTS: In contrast to previous reports suggesting that fluoroquinolone-associated PNS events are mild and short-term, 36 of the 45 cases reported severe events that typically involved multiple organ systems. Although many newer cases are still evolving, symptoms had lasted more than three months in 71% of cases and more than one year in 58%. Onset of adverse events was usually rapid, with 15 (33%) events beginning within 24 hours of initiating treatment, 26 (58%) within 72 hours, and 38 (84%) within one week. Sixty courses of fluoroquinolones were prescribed: levofloxacin (n = 33 cases), ciprofloxacin (n = 11), ofloxacin (n = 6), lomefloxacin (n = 1), trovafloxacin (n = 1); in eight cases the same antibiotic was prescribed twice.

CONCLUSIONS: These cases suggest a possible association between fluoroquinolone antibiotics and severe, long-term adverse effects involving the PNS as well as other organ systems. The severity of these cases may reflect a different population than typically reported to drug companies or MedWatch, which often originate from healthcare providers. In contrast, Internet Web sites may provide a forum for patients experiencing adverse effects that have not resolved promptly. Further study is warranted. Meanwhile, the occurrence of PNS symptoms during fluoroquinolone therapy should prompt immediate discontinuation of the agent used.

KEY WORDS: adverse events, ciprofloxacin, fluoroquinolones, levofloxacin, lomefloxacin, ofloxacin, trovafloxacin.

The fluoroquinolone antibiotics are an important, frequently prescribed group of medications. Fluoroquinolone adverse events involving the central nervous system (e.g., dizziness, headache, seizures, psychosis) are well known.¹⁻¹¹ However, less recognized are fluoroquinolone-associated peripheral neuropathies, and only a few reports¹²⁻¹⁶ and one article¹⁷ have been published in the medical literature regarding such events, which are usually described as mild and of short duration.

In contrast, in recent years hundreds of reports involving fluoroquinolone-associated events involving the central nervous system (CNS), musculoskeletal system, and peripheral nervous system (PNS) have been posted on Inter-

net Web sites by patients or concerned family members. Many of these events are described as severe and long-lasting, causing substantial pain, impairment of functioning, and, in some cases, long-term disability. In order to provide a central forum for these people, in February 1999 the Quinolone Antibiotics Adverse Reaction Forum was established at www.geocities.com/quinolones/ to provide a central forum for individuals to self-report adverse events experienced in association with fluoroquinolones. The Web site also offers links to the National Institutes of Health and other relevant medically oriented Web sites, and encourages people to use its link to the Food and Drug Administration's (FDA's) MedWatch program for filing official reports. As of October, 2001, the site received more than 73 000 visitors and 5000 posts. With the assistance of members of this Web site, a survey of cases involving PNS

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symptomatology was conducted in order to examine the number and characteristics of these adverse events in this population.

Events since September 11, 2001, have heightened the importance of physicians' and the public's awareness of serious adverse effects associated with fluoroquinolones. Because of the current anthrax threat and the hoarding of ciprofloxacin by thousands of people, the benefits of this antibiotic and other fluoroquinolones must be weighed carefully and treatment must be undertaken judiciously. The media, generally, have presented only a few fluoroquinolone adverse effects, which are usually described as mild. One leading news magazine stated that a 30-day course of ciprofloxacin "wouldn't cause a healthy adult much direct harm" unless also taken with theophylline.¹⁸ There are anecdotal reports of people already taking ciprofloxacin prophylactically. The 45 cases presented in this article, as well as previous published articles about the neurotoxicity and effects of fluoroquinolones on musculoskeletal structures, should give patients and physicians pause before using fluoroquinolones without specific indication. Moreover, people need to know what to do if potentially serious fluoroquinolone adverse effects occur.

Methods

RECRUITMENT OF CASES

Forty-seven patient cases were obtained by posting a message requesting submission of cases involving PNS events for the purpose of a medical survey. One case was sent directly to the author, and five cases were forwarded from another fluoroquinolone-related adverse event Web site (the Tropicalpenguin Health Forum: <http://www.tropicalpenguin.com/health/forum/messages/241.html>).

INCLUSION OF CASES

All cases involving symptoms suggestive of peripheral neuropathies and fulfilling inclusion criteria described below were included. Acceptable symptoms included sensory abnormalities (tingling, numbness, prickling, pins/needles sensation, burning pain, "electrical" or shooting pain, skin-crawling sensation, hyperesthesia, hypoesthesia, allodynia, numbness), and motor abnormalities (weakness, twitching, fasciculations, tremors, spasms, contractions).

DATA REQUIRED

Cases were required to provide information that equaled or exceeded the standards of the FDA's MedWatch program. Information requested included name (or another identification for patients preferring anonymity), age, gender, weight; date antibiotic was taken, reason for antibiotic use, specific antibiotic used, dosage, duration; time of use until onset of symptoms; symptoms of the adverse events and the degree of discomfort and/or impact, if any, on normal functioning; duration of events; prior medical problems and/or medications; subsequent treatment, if any, for adverse events; whether a MedWatch report was submitted to the FDA.

IDENTIFICATION OF ADVERSE DRUG EVENT

Adverse events were defined according to the FDA's current definition: "an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacologic action of the drug or may be unpredictable in its occurrence."¹⁹ Likelihood of the event being associated with fluoroquinolone treatment was rated by the author ac-

ording to the Naranjo et al.²⁰ probability scale. Patients were asked about other possible causes of their events.

SEVERITY OF ADVERSE EFFECT

The author categorized the adverse drug events (ADEs) as follows: a mild ADE was associated with mild to moderate pain or discomfort lasting less than two weeks; a moderate ADE was associated with substantial discomfort and/or significant limitations in normal functioning lasting less than two months; a severe ADE was associated with severe discomfort and/or limitations in functioning that lasted more than two months.

CONFIRMATION OF INFORMATION

Information from each patient was entered and organized into a computer database. Each patient was E-mailed a copy of his patient information and asked to confirm its accuracy, as well as to provide missing information or explain unclear details. Patients were also requested to provide identifying information such as address and telephone number, electively.

EXCLUSION OF CASES

Cases that were not confirmed were excluded by the author. Cases that appeared equivocal or in which patients had other conditions or were taking other medications that might explain the adverse events were also excluded.

Results

Forty-five cases fulfilling all criteria were received. The specifics of 15 representative cases are listed in Table 1.

Based on established scales for assessing the probability of an event's relatedness to a prescribed treatment,²⁰ 31 cases fulfilled the criteria of possible adverse drug events: (1) the events represented recognized events with these drugs; (2) the events occurred in a credible temporal sequence with the treatment; (3) the events could not be reasonably explained by information provided about the patients' conditions or other factors. Six cases were rated as probable because, in addition to meeting the above criteria, withdrawal of the drug led to lessening of the events. Eight cases were rated as definite, because the patients experienced some symptom resolution after finishing an initial course of a fluoroquinolone, then experienced worsening of symptoms with repeated exposure to the same or another fluoroquinolone.

PATIENTS' CHARACTERISTICS

Of the 45 cases, 23 (51%) were women and 22 (49%) were men. The average age was 42 years (range 11–68). Of 39 patients providing details about their prior health status, 24 (62%) had no prior medical problems, 11 had one other medical disorder (28%), and four (10%) had two medical disorders. These disorders were generally mild and included chronic allergies/sinusitis (n = 5), controlled asthma (4), controlled hypertension (3), thyroid disorders (3), mild depression (2), osteoporosis (1), and mild immunoglobulin deficiency (1). The specific disorders that necessitated fluoroquinolone treatment are listed in Table 2.

Table 1. Fifteen Cases of Fluoroquinolone-Associated Events^a

Pt. Age/ Gender	Drug	Use	ADE Onset (d)	Symptom	Course	Treatment
32/F	Cip	UTI	1	tingling, anxiety	antibiotic stopped, effects quickly abated	none
11/F	Lev	bone infection	5	tingling, "electrical" pain in arms and legs	pain limited walking, symptoms disappeared 2 d after antibiotic stopped	none
39/M	Lev	prostate infection	20	diffuse tingling, skin-crawling sensation, numbness	moderate discomfort, nearly complete resolution over 14 mo	none
26/M	Lev	bronchitis	1	numbness, tingling, twitching, allodynia, anxiety	constant discomfort 1 mo, gradual improvement over 6 mo, anxiety remains	
40/M	Lev	UTI	4	tingling, burning pain, twitching, knee swelling, joint/muscle pain, odd smells	severe pains, function limited, gradually improved over 40 d, some symptoms persist	none
41/F	Lev ^b	sinusitis	2	diffuse numbness, allodynia, severe, muscle/joint pain	severe initially, greatly limited functioning, subsided over 2 wk	steroids helpful
32/M	Lev	prostate infection	1	numbness, tingling, shooting pain, severe tendon pain	disabling for several mo, unable to exercise for 6 mo, resolved after 2 y	NSAIDs minimally helpful
34/M	Lev ^b	prostate infection	5	numbness, muscle twitching, weakness, impaired coordination, increased sensitivity to temperatures, fatigue, multiple joint/muscle pain, palpitations, blurred vision, fear	severe for 4 mo, some symptoms persisting after 12 mo	diazepam partially helpful
31/F	Lev	sinusitis	3	diffuse tingling, burning pain, numbness, "pins/needles," twitching, multiple severe tendinitis, temperature intolerance	functioning limited initially, slow improvement, with some symptoms still lasting after 6 mo	none
53/M	Lev ^b	prostate infection	2	numbness, tingling, cramps, wrist pain, tremors, fatigue, joint/tendon pain	severe initially; some sensory symptoms continue, joint pain limits walking after 14 mo; nerve biopsy showed nonspecific damage	none
49/F	Ofi	pelvic infection	1	diffuse numbness, "pins/needles," burning pain, memory loss, impaired vision, joint pain, palpitations, diarrhea, stomach cramps, altered sense of smell, insomnia, tinnitus, severe panic attacks	functioning limited, work affected, some symptoms still present after 3 y	none
51/F	Lev	pelvic infection	2	"electrical" sensations, numbness, allodynia, multiple severe tendinitis, partial tear of Achilles tendon, memory problems, confusion, impaired concentration	Achilles tear required cast/crutches for 3 mo; memory problems and multiple tendinitis persisted after 1 y	NSAIDs not helpful; steroids helped tendinitis
56/F	Ofi, Cip	UTI	3	acute nocturnal onset of severe burning pain, numbness, twitching; "electrical" sensations, carpal tunnel syndrome, nightmares, confusion, tachycardia, 30-lb weight loss, muscle/joint pain, impaired hearing, altered sense of smell	initially went to ED; disabled, most symptoms have persisted 4 y	lorazepam helpful for some symptoms
44/F	Cip	bronchitis	4	numbness, allodynia, hyperesthesia, tremors, "electrical" sensations, diffuse burning sensation, tremors, twitching, disorientation, visual impairment, nausea, temperature intolerance, rash, palpitations	went to ED; multiple drugs unhelpful; remains disabled after 29 mo; tests confirmed nonspecific nerve damage	steroids worsened symptoms
38/M	Lom	prostate	14	severe twitching, numbness, "electrical sensations," tingling, pain, hyperesthesia, muscle/joint pain, fatigue, multiple CNS symptoms	disabled, most symptoms persisting after 6 y	multiple drugs not helpful

Cip = ciprofloxacin; CNS = central nervous system; ED = emergency department; Lev = levofloxacin; Lom = lomefloxacin; NSAIDs = nonsteroidal anti-inflammatory drugs; Ofi = ofloxacin.

^aSelected to represent the range of symptoms and severity among the 45 cases in this survey.

^bSecond course of levofloxacin; mild events unrecognized during first course.

ANTIBIOTIC USE

Levofloxacin was taken by 33 patients; ciprofloxacin, 11; ofloxacin, 6; lomefloxacin, 1; and trovafloxacin, 1. Overall, the 45 patients received 60 courses of fluoroquinolone antibiotics. Five patients received two different fluoroquinolones and one received three; in each of these cases, adverse events had occurred with the initial prescription. Eight patients received two courses of the same antibiotic; six of these patients described adverse events with their initial fluoroquinolone prescriptions.

The onset of adverse events was usually rapid, with 15 of the 45 patients' (33%) events beginning within 24 hours of initiating fluoroquinolone treatment, 26 (58%) beginning within 72 hours, 38 (84%) occurring within seven days, and 43 (96%) within 14 days. Events began while receiving fluoroquinolones in all 45 cases.

TYPES AND DURATION OF SYMPTOMS

Of the 45 cases, 21 (47%) reported both sensory and motor abnormalities of the PNS. Twenty (44%) reported only sensory abnormalities, and four (9%) reported only motor abnormalities.

Forty-two patients (93%) experienced symptoms involving systems outside the PNS; many experienced symptoms in multiple organ systems. CNS symptoms were reported in 78% of cases; musculoskeletal symptoms, 73%; special senses, 42%; cardiovascular, 36%; skin, 29%; and gastrointestinal, 18%. The nature of these events are listed in Table 3.

The duration of symptoms exceeded one month in 41 of 45 cases (91%), three months in 32 cases (71%), one year in 26 cases (58%), and 12 (27%) have exceeded two years' duration. One case has continued more than four years and another more than six years. These numbers are not final because some cases were relatively new and are still evolving.

Table 2. Disorders Requiring Fluoroquinolone Therapy^a

Disorder	Patients	
	n	%
Sinusitis	13	33
Prostatitis, epididymitis	9	23
Urinary tract infection	6	15
Pulmonary (asthma, bronchitis, pneumonia)	6	15
Postabdominal surgery	2	5
Inner ear infection	1	2.5
Toe infection	1	2.5
Bone infection	1	2.5

^aThirty-nine patients.

SEVERITY OF SYMPTOMS

Based on the severity scale defined in the *Methods* section, two cases were mild (4%), seven moderate (16%), and 36 severe (80%). The severity of symptoms caused 11 patients to seek assistance at emergency departments, and one patient went twice. Many patients offered unsolicited descriptions of impaired functioning or a severity of pain or other symptoms that appeared traumatic.

RECOGNITION OF ADVERSE EVENTS

Eighteen patients stated that their physicians either failed to recognize or dismissed the significance of their neu-

Table 3. Adverse Events Reported^a

System	Patients		Reported Events
	n	%	
PNS, sensory	41	91	tingling, numbness, prickling, burning pain, pins/needles sensation, "electrical" or shooting pain, skin crawling sensation, hyperesthesia, hypoesthesia, allodynia, numbness
PNS, motor	25	55	weakness, twitching, fasciculations, tremors, spasms, contractions
CNS	35	78	dizziness, malaise, weakness, impaired coordination, nightmares, insomnia, headaches, agitation, anxiety, panic attacks, disorientation, impaired concentration or memory, confusion, depersonalization, hallucinations, psychoses
Musculoskeletal	33	73	muscle pain, weakness, soreness; joint swelling, pain; tendon pain or rupture
Special senses	19	42	diminished or altered visual, olfactory, auditory functioning, tinnitus
Cardiovascular	16	36	tachycardia, shortness of breath, hypertension, palpitations, chest pain
Skin	13	29	rash, urticaria, hair loss, sweating, intolerance to heat and/or cold
Gastrointestinal	8	18	nausea, vomiting, diarrhea, abdominal pain
Other symptoms			
weight loss	3	7	
anemia	2	4	
difficulty urinating	1	2	
worsening of asthma	1	2	

CNS = central nervous system; PNS = peripheral nervous system.
^aAll patients (n = 45) reported at least one event involving the PNS. In addition, 42 patients (93%) reported events in other organ systems.

ropathies or more commonly recognized fluoroquinolone-associated events such as joint pain, tendon pain, or CNS symptoms. Mild adverse events often were not recognized. Four patients reported being told to continue taking the antibiotics despite complaining of adverse events.

TREATMENT

Eighteen patients reported receiving no medical treatment for these events. Twenty-seven respondents received medication therapy. Fourteen patients received nonspecific treatment such as antidepressant, antiinflammatory, hypnotic, or pain medication, usually with limited benefit. Ten patients received steroids; of these, five reported partial improvement of musculoskeletal symptoms, while two reported worsening of neurologic symptoms. Five patients received benzodiazepines, of whom three reported partial improvement. One patient received gabapentin, and experienced partial improvement. Many patients undertook their own treatment measures such as improving their diets and/or beginning or increasing their exercise, if symptoms allowed.

SUBMISSION TO MEDWATCH

Patients were asked whether they had filed reports to the FDA MedWatch program: 21 had filed a report, and two of these had filed two reports; 10 filed no report; one patient asked her physician to file a report but was not sure whether he did; 13 patients did not answer this question.

Discussion

USE OF CASES COLLECTED VIA INTERNET

The Internet has facilitated a volume and rapidity of communication that not even science-fiction writers imagined. Already, many physicians have had to review information of variable quality brought to them by concerned patients. In this article, the use of the Internet to conduct a survey naturally raises questions of reliability. However, all science begins with observation, and the Internet presents unique opportunities as a source of concentrated, elective, patient-based information not previously available.

Some precedent exists in the use of the Internet as a source of medically useful information. A common Web site and communication channel for patients with erythromelalgia, a rare and painful vascular disorder, spawned The Erythromelalgia Association (TEA); (available at www.erythromelalgia.com). This in turn facilitated the collection of data from the largest group of erythromelalgia patients ever assembled and the publication of a much-needed review article²¹ describing the diagnosis, pathophysiology, and treatment of this often-recalcitrant disorder.

Similarly, in the present study, a common concern about possible fluoroquinolone-related adverse events has led to the informal association of thousands of individuals report-

ing cases and/or sharing information in a manner that was impossible before the Internet. Thus, these and other Web sites may represent different populations than those reflected by traditional reporting mechanisms (FDA, drug manufacturers). With Internet cases, information is derived directly from patients, whereas reports to the FDA and manufacturers usually originate from healthcare providers. Internet cases are, therefore, likely to present a different perspective and different biases. It should be noted, however, that patient-based reporting is accepted, indeed encouraged, by the FDA, so these reports are a legitimate source of information. Indeed, the ability to contact patients to clarify and confirm information provided a degree of completeness of information often lacking in reports submitted to the FDA.

NEUROTOXICITY AND FLUOROQUINOLONE ANTIBIOTICS

CNS effects are the second most common type of adverse event reported with fluoroquinolones,^{9,22,23} occurring at an incidence of 1–7%.^{2-4,9,24-26} It is established that fluoroquinolones can be neurotoxic,^{2-4,7,27,28} and that these drugs can produce dose-related CNS excitation through inhibition of γ -aminobutyric acid (GABA) receptors,^{2,3,24,28,29} and perhaps *N*-methyl-D-aspartate or adenosine receptors.^{9,29} Fluoroquinolones lower seizure thresholds^{7,23,29} and impede neuromuscular transmission,³⁰ and they have been associated with seizures and psychoses.^{2,4,7-9,23,31} Interestingly, fluoroquinolone-associated seizures usually develop within a few days of commencing treatment,^{9,25} which is similar to the pattern reported here in which adverse events began within three to four days in 58% of cases and within seven days in 84%.

In contrast to CNS events, fluoroquinolone-associated PNS events are not widely recognized. Although adverse events such as paresthesias or neuropathies occurred at an incidence of <0.5–1%, according to manufacturers³¹; the manufacturers of levofloxacin (personal communication, Laura Mack RN, Ortho-McNeil Pharmaceuticals, April 24, 2001) and ciprofloxacin (personal communication, Steve Paine RPh, Bayer Corp., April 24, 2001) have received no postmarketing reports involving the PNS. The only previous report in the medical literature involving more than a few cases of fluoroquinolone-related neuropathies was published in 1996 by the Swedish Adverse Drug Reactions Advisory Committee.¹⁷ This report listed 37 cases of peripheral sensory disturbances submitted to the Swedish authorities over a period of seven years (1987–1993). Most of these events were mild and brief.

The present article describes a more serious problem, perhaps reflecting the reporting population. The 45 cases reflected here were provided voluntarily by patients motivated, in most incidences, by severe or persisting problems, and motivated enough to seek information via the Internet, to locate and communicate through the Web site, and to submit information to the author. These factors may explain the preponderance of severe cases in this survey and on Web sites for fluoroquinolone-related reactions that

differ markedly from previous published information.^{6,12,15-17} Thus, by attracting patients seeking information because of severe or persistent events, Internet groups may provide a different perspective on possible long-term events associated with fluoroquinolones as well as with other drugs.

The preponderance of cases involving levofloxacin cannot be explained by currently available information. The secondary Web site from which five cases were received consists mainly of cases involving levofloxacin, but the main Web site that provided 39 cases includes all fluoroquinolones. The preponderance of levofloxacin-associated cases also cannot be explained by prescribing trends: in 2000, 14 004 000 prescriptions were filled for ciprofloxacin; 9 958 000 were filled for levofloxacin.³² Thus, this trend may reflect a reporting bias or perhaps a previously unrecognized tendency toward greater neurotoxicity with levofloxacin.

TREATMENT CONSIDERATIONS

The large number of patients stating that their adverse reactions were missed or dismissed by their physicians raises the question of whether some physicians are unaware that fluoroquinolones have been associated with serious nervous system effects. Alternately, the physicians may have been unconvinced that the events were related to treatment. In some cases, the severity and multiplicity of these symptoms may have produced a confusing picture that suggested unrelated conditions, especially since fluoroquinolone-associated neuropathies are typically described in the medical literature as mild and reversed by discontinuation of the drugs.^{6,28,33} At the same time, the Internet population may be biased toward patients dissatisfied with their treatment and/or outcomes. It may be that there are as many or even more patients encountering similar problems, but who obtained better outcomes or were satisfied with their physicians' responses.

Clarification of these issues is beyond the scope of this survey. For now, it appears that immediate discontinuation is required for patients presenting with fluoroquinolone-related peripheral neuropathies (or CNS or musculoskeletal symptoms),³⁴ and further antibiotic therapy should be provided from a different antibiotic group. Physicians should be aware that fluoroquinolone-associated events can occur after a single dose.³⁵ However, in this survey, the majority of severe cases occurred in patients who continued or restarted fluoroquinolones after adverse events had occurred. Thus, prompt recognition and withdrawal appears imperative, especially because there is no recognized treatment for these events and, according to this survey, supportive treatment is often not highly effective.

Because fluoroquinolones compete for GABA receptors, the use of benzodiazepines may be warranted. In this survey, one patient reported mild improvement with clonazepam, a benzodiazepine with a strong affinity for GABA receptors.

Because of interactions involving the nervous system, patients should be cautioned about using caffeine-containing

foods^{4,32,36-38} or nonsteroidal antiinflammatory drugs^{4,15,23,24,31} with fluoroquinolones.

LIMITATIONS AND FUTURE STUDY CONSIDERATIONS

Many of the limitations of this study have already been stated. As with the FDA's MedWatch program, this survey obtained voluntary reports from people not directly seen or evaluated by the author, and the submitted information reflected the perspectives of the patients reporting it. These perspectives included interpretations of causality, which may have differed from the perspectives of some patients' physicians. Moreover, the reports in this survey emanated from a subpopulation of patients motivated to seek information via the Internet and motivated to volunteer for the survey.

Because of its limitations, this article is not intended or capable of establishing a cause-effect association between the described events and fluoroquinolone therapy, and no statistical tests were performed. Instead, the purpose of the article is to report the existence of large concentrations of patients with strikingly similar descriptions of possible fluoroquinolone-associated adverse events of significant severity and chronicity, and to suggest that further, more formal scrutiny is warranted. It is also the intention of this article to alert healthcare providers of the possible association of fluoroquinolone therapy with these events in a population of generally young, previously healthy and active people.

Summary

Fluoroquinolones are important members of medicine's arsenal of antibiotics. Serious ADEs involving the CNS and musculoskeletal systems have been reported but are considered infrequent. Mild ADEs involving the PNS have also been reported. This article, which presents a survey of a different population (with mainly serious, long-term symptoms) from a different source (the Internet), offers a new and different perspective on fluoroquinolone-related events involving the PNS. Further, better controlled investigation is warranted. The FDA should also review and report on its cases relating to fluoroquinolone antibiotics. If the occurrence of fluoroquinolone-associated ADEs of this severity and duration is confirmed, physicians need to be informed and warnings might be considered for these drugs' product information. In the meantime, healthcare providers may need to be vigilant regarding ADEs associated with fluoroquinolones, and even mild events involving the nervous or musculoskeletal systems should prompt immediate discontinuation.

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