EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 6
210-220
Year: 2019

NEUROTOXIN EFFECT & VARIOUS MEDICINAL USES OF FLUOROQUINOLONES

Aljabir Jondi Kartan*[1], Ankita Sharma*[2], Kaushal K. Chandrul*[3]

[1]Pharmacy Graduate Pharmaceutical Science, Mewar University, Chittorgarh Rajasthan, India, 312901.
[2]Assistant Professor and Researcher at Faculty of Pharmaceutical Sciences, Mewar University, Chittorgarh, Rajasthan, India, 312901.
[3]Dean, Faculty of Pharmaceutical Science, Mewar University, Rajasthan, India, 312901.

***Corresponding Author: Aljabir Jondi Kartan**
Pharmacy Graduate pharmaceutic al Science, Mewar University, Chittorgarh Rajasthan, India, 312901.

Article Received on 09/04/2019 **Article Revised on 30/04/2019** **Article Accepted on 21/05/2019**

ABSTRACT
With increasing use of fluoroquinolones, there have been numerous reports of central nervous system adverse effects differing with individual fluoroquinolones. Structure toxicity relationship shows that the C-7 substituent on the quinolone nucleus plays an important role in the central nervous system effects of these compounds by inhibiting the interaction of gamma amino butyric acid with the receptors. Study done in healthy human volunteers has demonstrated the reversal of increased central nervous system activity induced by ofloxacin with midazolam. Risk factors for the neurotoxicity include elderly age, presence of central nervous system disorder, impaired renal function and drug-drug interactions. While the central effects are more common with ciprofloxacin and ofloxacin, these have also been reported with levofloxacin which has a better structure toxicity profile. Knowledge of these reversible and potentially avoidable adverse effects of fluoroquinolones can prevent misdiagnosis, unnecessary investigation and improper medication. A robust pharmacovigilance mechanism is essential for determining and monitoring the CNS adverse effects of existing and newer fluoroquinolones.

KEYWORDS: Fluoroquinolones, neurotoxicity, Toxicity, CNS, seizures.

INTRODUCTION
Fluoroquinolones (FQs) are commonly used antibiotics both in inpatient and outpatient settings. Their therapeutic use ranges from the common respiratory, urinary tract and gastrointestinal infections to management of drug resistant tuberculosis and febrile neutropenia in immunocompromised patients.[1] Significant features of this group of antibiotics include their wide antibacterial spectrum, less frequent dosing interval and relatively better patient tolerability. A study of antibiotic use in the public and private healthcare facilities and private retail pharmacies in New Delhi, India showed that the betalactam antibiotics and fluoroquinolones were the most commonly prescribed antibiotics. Ofloxacin, ciprofloxacin, levofloxacin, and norfloxacin were the most commonly prescribed fluoroquinolones.[2] A similar study of antibiotic use in acute diarrhea showed inappropriate use of fluoroquinolones, including in children.[3] The high consumption rates of FQs coupled with the problem of potentially inappropriate prescriptions can result in increased incidence of adverse effects and antimicrobial drug resistance besides the economic implications involved.

Of particular importance is the central nervous system (CNS) adverse effect of FQs which seems to be under recognized.[4] With increasing use of fluoroquinolones, there have been numerous reports of CNS adverse effects differing with individual fluoroquinolones. CNS-related adverse events have been reported to be higher in association with quinolone use than with the use of other systemic antimicrobials.[5] Also important is the fact that the CNS adverse events are avoidable to a large extent by knowing the predisposing drug and patient characteristics. The impact of adequate prescriber awareness and the consequent patient education regarding these factors can be enormous considering the widespread use of these antibiotics.

Hence the aim of the present article is to review the literature on the mechanism(s) of neurotoxicity and clinical aspects of central nervous system adverse effects of FQs.

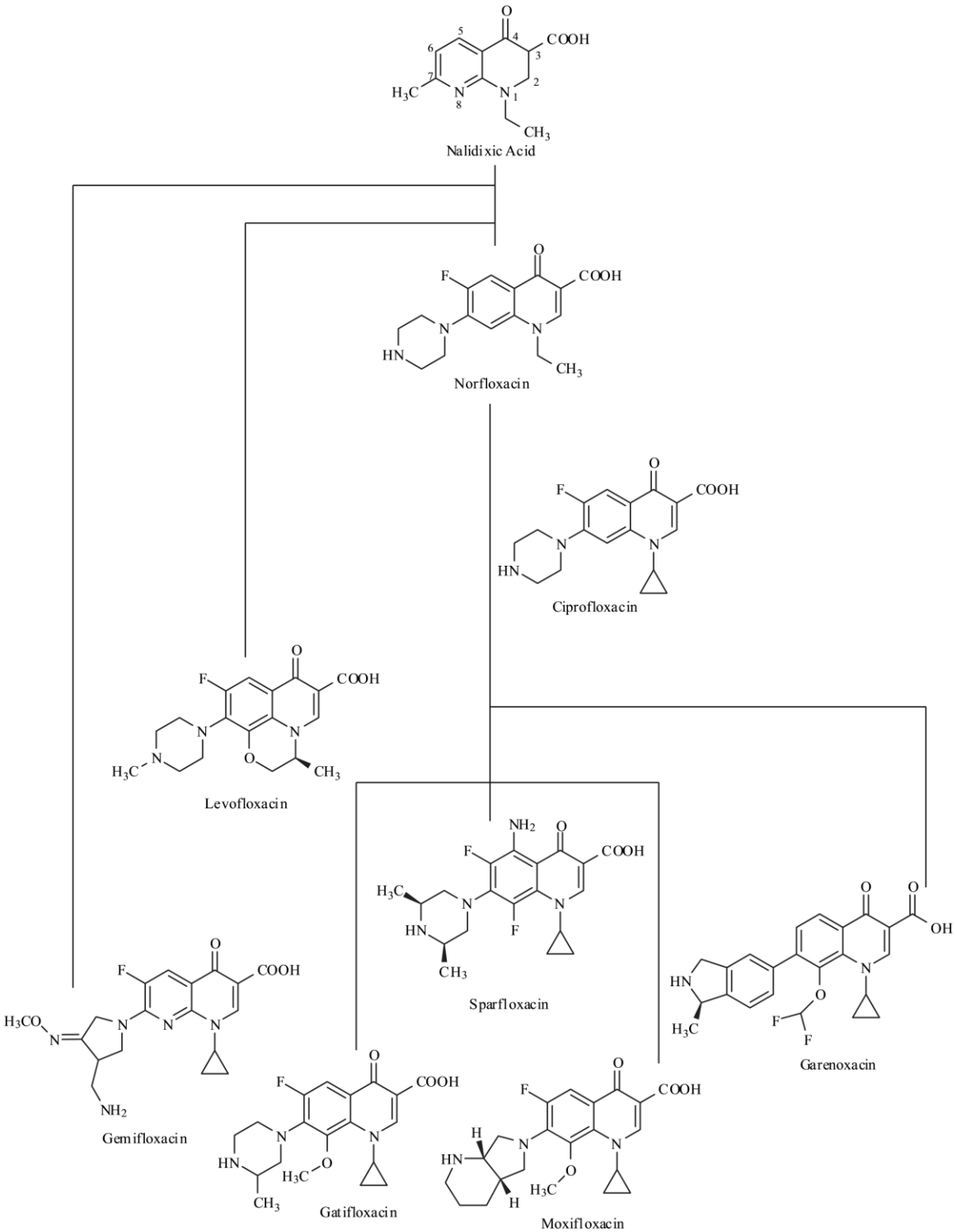

Fig. (1). Evolution of commonly used fluoroquinolones.

Can sometimes be drawn from studies of their eukaryotic counterpart. Differences between the two bacterial enzymes may reflect different chromosomal functions or locations; therefore, quinolone-containing complexes with one target may be more cytotoxic than with another. Such information potentially contributes to a rationale for choosing one compound over another for treatment of a particular pathogen, since differences in target preference could affect potency.

A central feature of fluoroquinolone resistance is that it develops in a step-wise fashion. Lowered susceptibility has been associated with changes in proteins that reduce the intracellular drug concentration, in proteins that protect the target enzymes from attack, and in the topoisomerases themselves. These changes probably arise spontaneously in members of large bacterial populations; the mutants are then selectively enriched by suboptimal quinolone treatment. Slowing or reversing

this process may require strategic changes in how fluoroquinolones are administered.

List of FDA-Approved Fluoroquinolones for Systemic Use

Brand Name	Active Ingredient
Avelox	moxifloxacin[+]
Baxdela	delafloxacin
Cipro	ciprofloxacin[+]
Cipro extended-release[±]	ciprofloxacin extended-release
Factive	gemifloxacin[+]
Levaquin	levofloxacin[+]
Ofloxacin (Generic brand)[±]	ofloxacin

FLUOROQUINOLONE RESISTANCE

Fluoroquinolone resistance is characterized by the gradual accumulation of mutations that lower intracellular drug concentration and/or sensitivity of the target DNA topoisomerases. With two exceptions[137, 138], the mutations reported to date have been chromosomal. The gradual accumulation of resistance causes surveillance studies to underestimate the development of resistance, since strains can contain resistance mutations and still be considered clinically susceptible. The underestimation problem may be compounded by the observation that some of the low-level resistance mutations are associated with an increased propensity for attaining additional resistance determinants. Thus resistance can appear to arise suddenly even though it is intrinsically a gradual process. One consequence is that surveillance studies can give a false sense of security. Examples in which the prevalence of resistance is already high are listed in Table (**2**).

Understanding resistance requires identification of the sources of resistance. One is likely to be the clinical use of the compounds [139], since use correlates with resistance for other antibacterial agents [140]. During the 1990s fluoroquinolone usage increased, and for that reason alone we would expect the prevalence of resistance to have increased (in the United States fluoroquinolone prescriptions increased about 9% per year between 1990 and 1998; in 1998 they reached almost 13 million [141], and by 2001 they reached 30 million annually (G. Tillotson, personal communication)). Another source is likely to involve agricultural use [142], since agricultural resistance can develop quickly. For example, within 2 years after the introduction of enrofloxacin in Denmark, ciprofloxacin resistance was found in *E. coli* isolated from cattle and in *Staphylococcus hyicus* obtained from pigs [143]. By 1998 30% of the *S. aureus* isolates obtained from poultry in Denmark were ciprofloxacin-resistant [144]. Increased and *Campylobacter* [146] is also blamed on agricultural prevalence of resistance among isolates of *Salmonella* [145] usage of fluoroquinolones.

Table 2. Quinolone Resistance Among Selected Bacterial Pathogens.

Pathogen species	Antibacterial agent	Geographic location	Percent nonsusceptible[a]	Reference
Campylobacter species				
	Fluoroquinolone	Denmark	20 (1999)	[146]b
		Italy	35 (1998)	[146]b
		Spain	70 (1998)	[146]b
		Thailand	83 (1995)	[146]b
		United States	20 (1995)	[146]b
Escherichia coli				
	Fluoroquinolone	Beijing	50-60 (1997-8)	[210]
		Greece	4-13 (1997)	[267]
		Hong Kong	16 (1997)	[268]b
		Korea	24 (1997)	[269]
		Venezuela	21 (1997-8)	[270]
Hemophilus influenzae				
	Ciprofloxacin	Spain	2 (1996-97)	[271]
Klebsiella pneumoniae				
	Ciprofloxacin	Croatia	25 (1990-5)	[272]
		Venezuela	16 (1998-99)	[273]
Mycobacterium tuberculosis	Ofloxacin	Spain	6 (1998?)	[260]
		Philippines	27 (1995-00)	[261]
Neisseria gonorrhoeae				
	Ciprofloxacin	India	6 (1999)	[215]b

		Japan	62 (1993-7)	[212]
Pseudomonas aeruginosa				
	Ciprofloxacin	Croatia	66 (1990-5)	[272]
		Europe	23 (1997)	[274]
		Latin America	26 (1997)	[275]
		Taiwan	13 (1998)	[276]
		United States	12 (1997)	[275]
Shigella species				
	Nalidixic acid	Bangladesh	60 (1990)	[277]b
Staphylococcus aureus				
	Ciprofloxacin	Brazil	98 (2000)	[278]
		Europe	96 (1997-98)	[279]
		Global	>70 (1997-98)	[280]
		United States	73 (2000)	[281]
Streptococcus pneumoniae				
	Levofloxacin	Hong Kong	13 (2000)	[240]
Vibrio cholerae				
	Nalidixic acid	India	98 (1994)	[282]b
	Ciprofloxacin	India	39 (1999)	[282]b

[a]The data are listed without distinction among types of patients, types of tissues infected, or local origin (nosocomial or community-acquired). Numbers in parentheses indicate year of determination. [b]Indicates time course reported.

The source of resistance can also be considered from a molecular perspective. Errors in DNA replication and repair cause mutants to be present in bacterial populations containing more than 10^7 cells; consequently, fluoroquinolone treatment need only enrich the mutant subpopulation for resistance to develop. Error rate is increased by faulty replication proteins called mutators (for example, in *E. coli* the Pol III mutator *dnaQ-49* creates a deficiency in the proofreading activity of DNA polymerase). Mutators occur among a variety of bacterial species [147-150], generally arising spontaneously under weak selection [151].

The quinolones are themselves mutagenic. One suggestion is that they induce mutations through the generation of free radicals, since the mutagenic effect of norfloxacin, nalidixic acid, and pipemidic acid is blocked by β-carotine [152], a scavenger of free radicals. Another is that the ternary complexes are misrepaired. To address this idea, quinolone mutagenicity has been examined by the Ames test [153-155]. In one study [154] the vast majority of mutations created were deletions, which would be consistent with misrepair of quinolone-topoisomerase-DNA complexes. When the test was set up to reveal reversions, excision repair and error-prone repair appeared to be involved [154]. These data are consistent with the hypothesis that induction of the SOS response is mutagenic [153, 156]. However, blocking this response by a *recA* mutation of *M. smegmatis* or by a *lexA* (Ind$^-$) mutation of *E. coli* has little effect on the frequency at which resistant mutants are recovered (J. Zhou and X. Zhao, unpublished observations). Thus it is not clear what fraction of mutants are drug-induced. For the purpose of the present discussion we assume that resistance develops largely from replication errors arising prior to drug treatment plus the subsequent dissemination of resistant strains.

Long-Term Adverse Reactions Caused by Fluoroquinolones

Fluoroquinolones (FQ) belong to the group of broadspectrum antibiotics, effective for both gram-negative and gram-positive bacteria. The most frequently prescribed drugs are ciprofloxacin (CIP), norfloxacin (NOR), and levofloxacin (LEV). FQs employ their antibacterial effect by preventing bacterial DNA from unwinding and duplicating which takes place by inhibition of bacterial topoisomerase and gyrase. For the last three decades, FQs played an important role in treatment of serious bacterial infections, especially hospital acquired infections. However, due to the possibility of serious side effects, these drugs are not currently first-line medicines and their use becomes more restrictive and limited. FQs should be reserved for those who do not have alternative treatment options.

In 2016, the US Food and Drug Administration (FDA) updated warnings, using next “black box” for oral and injectable FQs. The authors showed that FQs, when used systemically, are associated with disabling and potentially permanent serious side effects. These side effects can involve the disruption of tendons, joints, muscles, nerves, nervous system disturbances, and even

induction of type 2 diabetes. Due to the increasing number of reports about FQ toxicity and long-term complications, FDA has introduced significant restrictions on their use in recent years, particularly in children and in people aged 65 years.

1.1. Tendon Rupture. FQs are associated with a significant risk of tendonitis and tendon rupture. Stephenson et al.[1] showed in their review the incidence of tendon injury among those taking FQs to be between 0.08 and 0.2%. In 2014, Lewis and Cook[2] proved that FQ-related tendinopathy is a complication of treatment with this family of antibiotics and it is usually linked with 1 or more synergistic factors: male sex, age, renal disease, rheumatic disease, coprescription of corticosteroid, and physical activity. For this reason, some sport medicine specialists have advised avoidance of FQs for athletes. Some authors, for example,[3, 4] proved that chronic renal disease, concomitant use of corticosteroids, and age >60 years are known risk factors for FQ induced tendinopathies. Concluding, FQs are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy.

1.2. Nervous System Disturbances. Taking FQs is associated with their neurotoxicity as well.[5–8] The main symptoms being correlated to FQ treatment include insomnia, restlessness, and, rarely, seizure, convulsions, and psychosis.[9–11] Many reports point to chronic persistent peripheral neuropathy to be generated by FQs.[12–18] Cohen[19] showed that a possible association between FQ and severe, long-term adverse effects involving the peripheral nervous system as well as other organ systems is observed.

1.3. Cardiotoxicity. Stahlmann and Riecke[20] showed that FQs prolong the heart's QT interval by blocking voltagegated potassium channels. In some cases, this can be a life-threatening condition because prolongation of the QT interval can lead to torsades de pointes, a life-threatening arrhythmia. Statistically, significant risk factors for clinically significant changes in QTs were hypokalemia and a left ventricular ejection fraction<55%.

1.4. Hepatotoxicity and Nephrotoxicity. The other adverse reactions generated by FQs include hepatotoxicity[21] and nephrotoxicity[22] Golomb et al.[23] reported a caseseries study and showed the potential occurrence of serious, persistent, and delayed multisymptom serious side effects apparently triggered by FQ use causing severe functional compromise and disability in previously vigorous, healthy individuals. In this study, Golomb et al. described patients who developed new-onset symptoms during and following FQ use. Domains of serious and persistent sequels included the better-recognized tendon and muscle issues but extended to the well-reported but still often unappreciated potential for cognitive, psychiatric, peripheral nervous, and gastrointestinal issues as well as endocrine issues.

1.5. Diabetes Mellitus. Telfer[24] conducted interesting study about FQ intake and development of type 2 diabetes mellitus (T2DM). They hypothesized that FQs induce an intracellular Mg^{2+} deficit that can lead to insulin resistance. Their data suggests that FQ exposure predisposes an individual to develop diabetes. He also showed a strong correlation between the increase in FQ application in the US in years 1990–2012 and the increase in T2DM incidences in subsequent years which suggests a large part of T2DM to be maybe generated by FQ exposure.

1.6. FQ-Associated Disability. In 2016, Kaur et al.[8] conducted basic science and clinical investigations of a newly identified adverse drug reaction, termed FQ-associated disability (FQAD). They proved that severe toxicities that develop when cancer patients receive supportive care drugs such as FQs are important, yet difficult to understand, detect, and to communicate to clinicians. Their findings supported recommendations of the FDA's advisory committee. Revision of FQ-product labels should be considered to include prominent descriptions of a newly identified FQ-associated long-term toxicity.

Concluding, patients with impairments of the CNS (e.g., epilepsy or arteriosclerosis), prolongation of the QT, elderly persons, and individuals with concurrent use of glucocorticoids or chronic renal diseases should not be treated with FQs. FQs are contraindicated in children because they cause destruction of the immature joint cartilage in animals. The use in pediatrics is restricted to life-threatening infections.

Mechanistically, fluoroquinolone resistance arises from changes in cell permeability, drug efflux, target-protecting proteins, and target enzymes. So far there is little evidence that bacteria contain enzymes that degrade the compounds (such enzymes have been observed in fungal systems [157]). In general, target enzyme mutations reduce susceptibility more than the other mutation types, although the additive effects of non-target alleles can produce high-level resistance [158].

Therapeutic Conclusions

The treatment of the FQAD, especially that lasting for many years, is a very difficult therapeutic problem. The effectiveness of different therapies carried out on patients is rather low. A large number of patients suffers from chronic tiredness, tendinopathies, neuropathies, and lack of sleep, even more than 12h/24 h. Understanding all the molecular mechanisms of the FQ activity in the cell is the urgent aim for the current science to find methods helping these people.

The main question that arises here concerns the reasons of chronicity of FQAD symptoms which last for many years, sometimes, even after a standard 5-day FQ treatment. 3 reasons can be taken into consideration.

(a) Long-lasting OS destroys the mitochondrial DNA and the newly synthesized proteins creating cytochrome complexes are disturbed in their structure leading to permanent electron leakage and OS.
(b) The complexes of FQ with proteins and cations areso stabile that they exist in the cells by many years disturbing energy production and epigenetics.
(c) Epigenetic changes in gene regulation become persistent many years of FQ application even in the case of lack of FQ in the cell.

The answer, which of these three possible reasons contribute to the chronicity of FQAD symptoms, is of high importance with respect to the problem of effective treatment of this state. The research answering these questions must be performed as fast as possible.

In the case of mtDNA destroying, the treatment is difficult and it must focus on the stimulation of mitochondrial replication. The more destroyed mitochondria must be removed and the less destroyed must replicate in order to substitute for the removed ones and to reduce the total LEC. After many replications, the most healthy mitochondria would dominate the cell. The final effect would depend on the state of the most healthy mitochondrium in the cell. The second possibility is to increase the ratio of cell exchange in the given tissue. The cells with more destroyed mitochondria must be shifted to apoptosis while more healthy cells must substitute them. This process, however, cannot take place in the central nervous system and muscles because the cell exchange is close to zero in these tissues. Also, the collagen exchange is very low causing the tendon regeneration to be a difficult and long-lasting problem.

If new research would confirm the existence of FQs in the cells and mitochondria in the amounts making possible their permanent interactions with proteins and cations even after many years of FQ application, the research must focus on methods on how to remove FQs from strong protein and cation complexes. The simplest way seems to be the application of increased doses of metal cations Fe^{2+}, Cu^{+}, Mn^{2+}, Zn^{2+}, and Mg^{2+} which are natural FQ-competitors for proteinbinding sites. It should be pointed that bivalent metal ions enter the cell to some degree due to the negative membrane potential of the cell and, next, enter the mitochondria.

Table 1: The conversion of Nernst equation $c_{in}/c_{out} = \exp(\Delta V z F/RT)$ for bivalent ions as Mg^{2+}, Mn^{2+}, Fe^{2+}, and Zn^{2+} shows strong relation between the actual membrane potential and ability of the cell/mitochondrium to attract and absorb the ions into the cell/mitochondrium. Reduced membrane potential ΔV is a strong factor which hinders entering bivalent cations to the cell. However, the detailed mechanisms of individual ion transport must be analyzed.

$\Delta V/\Delta\Psi_m$	Equilibrium c_{in}/c_{out} gradient (z =2 and T =310 K)
−160 mV	160.000x
−140 mV	36.000x
−110 mV	3.800x
−90 mV	850x
−70 mV	190x
−50 mV	42x
−30 mV	9x

Mechanisms of fluoroquinolone induced neurotoxicity

Structure toxicity relationship shows that the C-7 substituent on the quinolone nucleus, particularly pyrrolidine or piperazine, plays an important role in the CNS effects of these compounds.[6] The CNS excitatory action of quinolones is based on the inhibition BDZ-$GABA_A$ receptor complex, particularly binding of gamma amino butyric acid (GABA) to the receptors. This mechanism is also shared by the betalactam antibiotics.[7] Quinolones containing 7piperazine (e.g., ciprofloxacin, norfloxacin) and those containing 7-pyrrolidine (e.g., tosufloxacin and clinafloxacin) have increased epileptogenic potential while substituted compounds containing 7piperazinyl– or 7-pyrollidinyl (e.g., levofloxacin) are associated with reduced seizure-causing potential. Gemifloxacin, levofloxacin, and moxifloxacin lack the specific structure-toxicity relationships noted to induce seizures.[8] The nature of C-7 substituent may also determine the interaction with non-steroidal antiinflammatory drugs (NSAIDs) and theophylline which can potentially increase the chances of seizures. Other receptors possibly involved in the CNS excitatory effects include N-methyl-D-aspartate, adenosine and amino acid receptors while effects on dopamine and opioid receptors has also been suggested.[9] A study done in healthy human volunteers confirmed the CNS stimulant action of ofloxacin as evidenced by the electroencephalographic changes.[10] After administration of flumazenil following ofloxacin the effects were even pronounced indicating an increased CNS activity. The ofloxacin induced increased CNS activity was completely reversed following administration of midazolam. Hence administration of benzodiazepine (BZD)-agonists might be useful in the treatment of fluoroquinolone induced neurotoxic events.

While the effect on the GABA receptor is well established it is likely that it is coupled with other mechanism(s) that increase the penetration of FQs into

the CNS to produce the toxicity. The lipophilicity of FQs depends on the individual compound. However, CNS penetration of FQs does not always correlate with the potential for epileptogenicity. In contrast to ciprofloxacin, ofloxacin has an increased CNS permeability of 50% of the serum concentration, though less cases of neurotoxicity have been reported for ofloxacin than for ciprofloxacin.[4, 11] Ofloxacin has a serum/plasma ratio of 47-87%. However, at therapeutic doses the serum concentration achieved is insufficient to produce adequate CSF levels necessary to produce adverse effects.[10] Abnormal state of blood brain barrier can increase the CNS penetration. Also, uneven distribution of the drug can result in higher concentration in specific areas of the brain.[10] Impaired renal function is associated with increase in elimination half-life and area under the curve, and a decrease in renal and total clearance.[12] Accumulation of FQs may occur particularly in the elderly.[10]

Clinical aspects of fluoroquinolone induced neurotoxicity.

CNS disturbances are second most commonly reported adverse events with FQs.[13] The overall incidence of these reports varies from 1% to 3.3%.[4, 8, 10] The most commonly reported symptoms include headache, dizziness and drowsiness. These usually occur on the first day of and resolve after discontinuation of the drug therapy. Other, less commonly reported, CNS events have included agitation, delirium, confusion/ encephalopathy, acute organic psychosis, seizures and abnormal vision.[4, 8] Seizures have been reported more frequently among individuals predisposed to epileptic seizures, cerebral trauma and anoxia.[8] The reported overall trend in incidence of drug-related CNS adverse events is as follows norfloxacin> ciprofloxacin> ofloxacin>levofloxacin.[11]

Patients who have received both fluoroquinolones and either theophylline or certain nonsteroidal antiinflammatory drugs are predisposed to develop seizures.[8] Ciprofloxacin has been shown to decrease the metabolic clearance of theophylline and caffeine. It is advisable to use non-interacting quinolones such as ofloxacin or norfloxacin or to measure theophylline levels and reduce caffeine intake where appropriate.[14] A synergistic inhibitory effect of fluoroquinolones and several NSAIDs has been observed on the binding of the neurotransmitter GABA.[14] Elderly patients should be monitored carefully for the CNS symptoms. It is likely that many signs of possible adverse reactions, such as confusion, weakness, loss of appetite, tremor or depression, are often mistakenly attributed to old age and remain unreported.[15] Oro-facial dyskinesias have also been reported with ciprofloxacin and ofloxacin, in the absence of a metabolic abnormality and at extremes of age.[16, 17] A tourette-like syndrome has also been described with ciprofloxacin implicating a possible interaction with the central dopaminergic system.[18]

While the CNS effects are more common with ciprofloxacin and ofloxacin, these have also been reported with levofloxacin which has a better structure toxicity profile.[4,19]

SUMMARY

The structure toxicity relationship of fluoroquinolones provides unique opportunity for the design and development of new quinolone derivatives with expanded antibacterial activity and better pharmacokinetics without the CNS effects. The reversal of CNS effects of FQs with the use of BZD in healthy volunteer study provides a therapeutic basis for their use in the management of FQ induced CNS adverse effects. The prescriber should be alert regarding the possibility of drug-drug interaction between FQs and other CNS active drugs, theophylline or NSAIDs. Other risk factors include elderly patients, those with CNS disorder and impaired renal function. Knowledge of these reversible as well as potentially avoidable CNS adverse effects of FQs can prevent misdiagnosis, unnecessary investigation and improper medication. Proper patient education will also help in avoiding unnecessary delay in reporting of symptoms in cases of psychiatric symptoms. Since the structure toxicity relationship alone is inadequate to predict the CNS effects of existing and newer FQs a robust pharmacovigilance mechanism is essential for determining and monitoring the CNS adverse effects.

ACKNOWLEDGEMENT

I would like to express my very great appreciation to Mrs. Ankita sharma (assistant professor and researcher at faculty of pharmaceutical science) for her valuable and constructive suggestions during the planning and development of this article. Her willingness to give her time so generously has been very much appreciated. #NH-79, Gangrar, Chittorgarh, rajastathan, India.

REFERENCES

1. Gellert, M.; O'Dea, M.H.; Mizuuchi, K.; Nash, H. DNA gyrase: an enzyme that introduces superhelical turns
2. into DNA. Proc. Natl. Acad. Sci. U.S.A, 1976; 73: 38723876.
3. Kato, J.-I.; Nishimura, Y.; Imamura, R.; Niki, H.; Hiraga, S.; Suzuki, H. New topoisomerase essential for chromosome segregation in E. coli. Cell, 1990; 63: 393404.
4. Mizuuchi, K.; Fisher, L.M.; O'Dea, M.; Gellert, M. DNA gyrase action involves the introduction of transient double-strand breaks into DNA. Proc. Natl. Acad. Sci. U.S.A, 1980; 77: 1847-1851.
5. Kreuzer, K.N.; Cozzarelli, N.R. Formation and resolution of DNA catenanes by DNA gyrase. Cell, 1980; 20: 245254.
6. Lu, T.; Malik, M.; Drlica-Wagner, A. C-8-methoxy fluoroquinolones. Res. Adv. in Antimicrob. Agents & Chemother, 2001; 2: 29-41.

7. Kim, O.; Ohemeng, K.; Barrett, J. Advances in DNA gyrase inhibitors. Exp. Opin. Invest. Drugs, 2001; 10: 199-212.
8. Heddle, J.G.; Barnard, F.; Wentzell, L.; Maxwell, A. The interaction of drugs with DNA gyrase: a model for the molecular basis of quinolone action. Nucleosides Nucleotides Nucleic Acids, 2000; 19: 1249-1264.
9. Drlica, K.; Zhao, X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol. Mol. Rev, 1997; 61: 377392.
10. Levine, C.; Hiasa, H.; Marians, K. DNA gyrase and topoisomerase IV: biochemical activities, physiological roles during chromosome replication, and drug sensitivities. Biochim. Biophys. Acta, 1998; 1400: 29-43.
11. Champoux, J.J. DNA topoisomerases: structure, function, and mechanism. Annu. Rev. Biochem, 2001; 70: 369-413.
12. Snyder, M.; Drlica, K. DNA gyrase on the bacterial chromosome: DNA cleavage induced by oxolinic acid. J. Mol. Biol, 1979;, 131: 287-302.
13. Pruss, G.J.; Manes, S.H.; Drlica, K. Escherichia coli DNA topoisomerase I mutants: increased supercoiling is corrected by mutations near gyrase genes. Cell, 1982; 31: 35-42.
14. Berger, J.M.; Gamblin, S.J.; Harrison, S.C.; Wang, J.C. Structure and mechanism of DNA topoisomerase II. Nature, 1996; 379: 225 - 232.
15. Fass, D.; Bogden, C.E.; Berger, J.M. Quaternary changes in topoisomerase II may direct orthogonal movement of two DNA strands. Nature Structural Biology, 1999; 6: 322-326.
16. MoraisCabral, J.H.; Jackson, A.P.; Smith, C.V.; Shikotra, N.; Maxwell, A.; Liddington, R.C. Crystal structure of the breakage-reunion domain of DNA gyrase. Nature, 1997; 388: 903-906.
17. Wigley, D.B.; Davies, G.J.; Dodson, E.J.; Maxwell, A.; Dodson, D. Crystal structure of an N-terminal fragment of the DNA gyrase B protein. Nature, 1991; 351: 624629.
18. Williams, N.; Howells, A.; Maxwell, A. Locking the ATPoperated clamp of DNA gyrase: probing the mechanism of strand passage. J. Mol. Biol, 2001; 306: 969-984.
19. Williams, N.L.; Maxwell, A. Locking the DNA gate of DNA gyrase: investigating the effects on DNA cleavage and ATP hydrolysis. Biochemistry, 1999; 38: 1415714164.
20. Kampranis, S.; Maxwell, A. Hydrolysis of ATP at only one GyrB subunit is sufficient to promote supercoiling by DNA gyrase. J. Biol. Chem, 1998; 273: 26305-25309.
21. Baird, C.L.; Harkins, T.T.; Morris, S.K.; Lindsley, J.E. Topoisomerase II drives DNA transport by hydrolyzing one ATP. Proc. Nat. Acad. Sci. U.S.A, 1999; 96: 1368513690.
22. Critchlow, S.E.; Maxwell, A. DNA cleavage is not required for the binding of quinolone drugs to the DNA gyrase-DNA complex. Biochemistry, 1996; 35: 73877393.
23. Kampranis, S.; Maxwell, A. Conformational changes in DNA gyrase revealed by limited proteolysis. J. Biol. Chem, 1998; 273: 22606-22614.
24. Kampranis, S.; Maxwell, A. The DNA gyrase-quinolone complex, ATP hydrolysis and the mechanism of DNA cleavage. J. Biol. Chem, 1998; 173: 22615-22626.
25. Morrison, A.; Cozzarelli, N.R. Site-specific cleavage of DNA by E. coli DNA gyrase. Cell, 1979; 17: 175-184.
26. Fisher, L.M.; Mizuuchi, K.; O'Dea, M.H.; Ohmori, H.; Gellert, M. Site-specific interaction of DNA gyrase with DNA. Proc. Natl. Acad. Sci. U.S.A, 1981; 78: 4165-4169.
27. Kampranis, S.C.; Maxwell, A. Conversion of DNA gyrase into a conventional type II topoisomerase. Proc. Natl. Acad. Sci. U.S.A, 1996; 93: 14416-14421.
28. Marians, K.; Hiasa, H. Mechanism of quinolone action: a drug-induced structural perturbation of the DNA precedes strand cleavage by topoisomerase IV. J. Biol. Chem, 1997; 272: 9401-9409.
29. Anderson, V.; Gootz, T.; Osheroff, N. Topoisomerase IV catalysis and the mechanism of quinolone action. J. Biol. Chem, 1998; 274: 17879-17885.
30. Bahng, S.; Mossessova, E.; Nurse, P.; Marians, K. Mutational analysis of Eshcerichia coli topoisomerase IV. J. Biol. Chem, 2000; 275: 4112-4117.
31. Anderson, V.; Zaniewski, R.; Raczmarek, F.; Gootz, T.; Osheroff, N. Action of quinolones against Staphylococcus aureus topoisomerase IV; basis for DNA cleavage enhancement. Biochem, 2000; 39: 2726-2732.
32. Cullen, M.; Wyke, A.; Kuroda, R.; Fisher, L. Cloning and characterization of a DNA gyrase A gene from Escherichia coli that confers clinical resistance to 4quinolones. Antimicrobial Agents Chemother, 1989; 33: 886-894.
33. Oram, M.; Fisher, M. 4-quinolone resistance mutations in the DNA gyrase of Escherichia coli clinical isolates identified by using the polymerase chain reaction. Antimicrob. Agents Chemother, 1991; 35: 387-389.
34. Sreedharan, S.; Oram, M.; Jensen, B.; Peterson, L.; Fisher, L. DNA gyrase gyrA mutations in ciprofloxacin-resistant strains of Staphylococcus aureus: close similarity with quinolone resistance mutations in Escherichia coli. J. Bacteriol, 1990; 172: 7260-7262.
35. Willmott, C.J.R.; Maxwell, A. A single point mutation in the DNA gyrase A protein greatly reduces binding of fluoroquinolones to the gyrase-DNA complex. Antimicrob. Agents Chemother, 1993; 37: 126-127.
36. Yoshida, H.; Nakamura, M.; Bogaki, M.; Ito, H.; Kojima, T.; Hattori, H.; Nakamura, S. Mechanism of

action of quinolones against Escherichia coli DNA gyrase. Antimicrob. Agents Chemother, 1993; 37: 839-845.
37. Barnard, F.; Maxwell, A. Interaction between DNA gyrase and quinolones: the effect of alanine mutations at A subunit residues Ser-83 and Asp-87. Antimicrob. Agents Chemother, 2001; 45: 1994-2000.
38. Lu, T.; Zhao, X.; Drlica, K. Gatifloxacin activity against quinolone-resistant gyrase: allele-specific enhancement of bacteriostatic and bactericidal activity by the C-8methoxy group. Antimicrob. Agents Chemother, 1999; 43: 2969-2974.
39. Yoshida, H.; Bogaki, M.; Nakamura, M.; Nakamura, S. Quinolone resistance-determining region in the DNA gyrase gyrA gene of Escherichia coli. Antimicrob. Agents Chemother, 1990; 34: 1271-1272.
40. Friedman, S.M.; Lu, T.; Drlica, K. A mutation in the DNA gyrase A gene of Escherichia coli that expands the quinolone-resistance-determining region. Antimicrob. Agents Chemother, 2001; 45: 2378-2380.
41. Dong, Y.; Xu, C.; Zhao, X.; Domagala, J.; Drlica, K. Fluoroquinolone action against mycobacteria: effects of C8 substituents on bacterial growth, survival, and resistance. Antimicrob. Agents Chemother, 1998; 42: 2978-2984.
42. Sindelar, G.; Zhao, X.; Liew, A.; Dong, Y.; Zhou, J.; Domagala, J.; Drlica, K. Mutant prevention concentration as a measure of fluoroquinolone potency against mycobacteria. Antimicrob. Agents Chemother, 2000; 44: 3337-3343.
43. Zhou, J.-F.; Dong, Y.; Zhao, X.; Lee, S.; Amin, A.; Ramaswamy, S.; Domagala, J.; Musser, J.M.; Drlica, K. Selection of antibiotic resistance: allelic diversity among fluoroquinolone-resistant mutations. J. Inf. Dis, 2000; 182: 517-525.
44. Cambau, E.; Borden, F.; Collatz, E.; Gutmann, L. Novel gyrA point mutation in a strain of Escherichia coli resistant to fluoroquinolones but not to nalidixic acid. Antimicrob. Agents Chemother, 1993; 37: 1247-1252.
45. Pan, X.-S.; Yague, G.; Fisher, L.M. Quinolone resistance mutations in Streptococcus pneumoniae GyrA and ParC proteins: mechanistic insights into quinolone action from enzymatic analysis, intracellular levels, and phenotypes of wild-type and mutant proteins. Antimicrob. Agents Chemother, 2001; 45: 3140-3147.
46. Yague, G.; Morris, J.; Pan, X.-S.; Gould, K.; Fisher, L.M. Cleavable-complex formation by wild-type and quinolone-resistant Streptococcus pneumoniae type II topoisomerases mediated by gemifloxacin and other fluoroquinolones. Antimicrob. Agents Chemother, 2002; 46: 413-419.
47. Ince, D.; Hooper, D. Mechanisms and frequency of resistance to premafloxacin in Staphylococcus aureus: novel mutations suggest novel drug-target interactions. Antimicrob. Agents Chemother, 2000; 44: 3344-3350.
48. Drlica, K.; Manes, S.H.; Engle, E.C. DNA gyrase on the bacterial chromosome: possibility of two levels of action. Proc. Natl. Acad. Sci. U.S.A, 1980; 77: 6879-6883.
49. Drlica, K.; Pruss, G.; Burger, R.; Franco, R.; Hsieh, L.-S.; Berger, B. Roles of DNA topoisomerases in bacterial chromosome structure and function, in The Bacterial Chromosome, Drlica, K. and Riley, M. Editors. American Society for Microbiology: Washington, 1990; 195-204.
50. Drlica, K.; Pruss, G.J.; Manes, S.H.; Chevalier, S.G. DNA topoisomerase mutations in bacteria, in Bacterial Chromatin, Gualerzi, C. Editor. 1986, Springer-Verlag: p. 52-63.
51. Chen, C.-R.; Malik, M.; Snyder, M.; Drlica, K. DNA gyrase and topoisomerase IV on the bacterial chromosome: quinolone-induced DNA cleavage. J. Mol. Biol, 1996; 258: 627-637.
52. Fournier, B.; Zhao, X.; Lu, T.; Drlica, K.; Hooper, D. Selective targeting of topoisomerase IV and DNA gyrase in Staphylococcus aureus: different patterns of quinolone-induced inhibition of DNA synthesis. Antimicrob. Agents Chemother, 2000; 44: 2160-2165.
53. Condemine, G.; Smith, C. Transcription regulates oxolinic acid-induced DNA gyrase cleavage at specific sites on the E. coli chromosome. Nucleic Acids Res, 1990; 18: 7389-7395.
54. Hiasa, H.; Yousef, D.; Marians, K. DNA strand cleavage is required for replication fork arrest by a frozen topoisomerase-quinolone-DNA ternary complex. J. Biol. Chem, 1996; 271: 26424-26429.
55. Pato, M.L.; Karlock, M.; Wall, C.; Higgins, N.P. Characterization of Mu prophage lacking the central strong gyrase binding site: localization of the block in replication. J. Bacteriol, 1995; 177: 5937-5942.
56. O'Connor, M.B.; Malamy, M.H. Mapping of DNA gyrase cleavage sites in vivo. Oxolinic acid induced cleavages in plasmid pBR322. J. Mol. Biol, 1985; 181: 545-550.
57. Lockshon, D.; Morris, D.R. Sites of reaction of Escherichia coli DNA gyrase on pBR322 in vivo as revealed by oxolinic acid-induced plasmid linearization. J. Mol. Biol, 1985; 181: 63-74.
58. Fisher, L.M.; Barot, H.A.; Cullen, M.E. DNA gyrase complex with DNA: determinants for site-specific DNA breakage. EMBO J, 1986; 5: 1411-1418.
59. Franco, R.; Drlica, K. DNA gyrase on the bacterial chromosome: oxolinic acid-induced DNA cleavage in the dnaA-gyrB region. J. Mol. Biol, 1988; 201: 229-233.
60. Yang, Y.; Ames, G. The family of repetitive extragenic palindromic sequences: interaction with DNA gyrase and histonelike protein HU, in The Bacterial Chromosome, K. Drlica and M. Riley, Editors. 1990, American Society for Microbiology, 211-225.

61. Yang, Y.; Ames, G. DNA gyrase binds to the family of prokaryotic repetitive extragenic palindromic sequences. Proc. Natl. Acad. Sci. U.S.A, 1988; 85: 88508854.
62. Boccard, F.; Prentki, P. Specific interaction of IHF with RIBs, a class of bacterial repetitive DNA elements located at the 3' end of transcription units. EMBO J, 1993; 12: 5019-5027.
63. Espeli, O.; Boccard, F. In vivo cleavage of Escherichia coli BIME-2 repeats by DNA gyrase: genetic characterization of the target and identification of the cut site. Mol. Microbiol, 1997; 26: 767-777.
64. Bachellier, S.; Perrin, D.; Hoffnung, M.; Gilson, E. Bacterial interspersed mosaic elements (BIMEs) are present in the genome of Klebsiella. Mol. Microbiol, 1993; 7: 537-544.
65. Bachellier, S.; Saurin, W.; Perrin, D.; Hofnung, M.; Gilson, E. Structural and functional diversity among bacterial interspersed mosaic elements (BIMEs). Mol. Microbiol, 1994; 12: 61-70.
66. Liu, L.; Wang, J. Supercoiling of the DNA template during transcription. Proc. Natl. Acad. Sci. U.S.A, 1987; 84:, 7024-7027.
67. Wu, H.-Y.; Shyy, S.-H.; Wang, J.C.; Liu, L.F. Transcription generates positively and negatively supercoiled domains in the template. Cell, 1988; 53: 433440.
68. Bendich, A. The form of DNA molecules in bacterial cells. Biochimie, 2001; 83: 177-186.
69. Hecht, R.M.; Pettijohn, D.E. Studies of DNA bound RNA molecules isolated from nucleoids of Escherichia coli. Nucleic Acids Res, 1976; 3: 767-788.
70. Sinden, R.R.; Pettijohn, D.E. Chromosomes in living Escherichia coli cells are segregated into domains of supercoiling. Proc. Natl. Acad. Sci. U.S.A, 1981; 78: 224228.
71. Staczek, P.; Higgins, N.P. Gyrase and topo IV modulate chromosome domain size in vivo. Mol. Microbiol, 1998; 29: 1435-1448.
72. Thornton, M.; Armitage, M.; Maxwell, A.; Dosanjh, B.; Howells, A.; Norris, V.; Sigee, D. Immunogold localization of GyrA and GyrB proteins in Escherichia coli. Microbiology, 1994; 140: 2371-2382.
73. Huang, W.M.; Libbey, J.; VanderHoeven, P.; Yu, S.X. Bipolar localization of Bacillus subtilis topoisomerase IV, an enzyme required for chromosome segregation. Proc. Natl. Acad. Sci. U.S.A, 1998; 95: 4652-4657.
74. Earnshaw, W.C.; Halligan, B.; Cooke, C.A.; Heck, M.M.S.; Liu, L.F. Topoisomerase II is a structural component of mitotic chromosome scaffolds. J. Cell Biol, 1985; 100: 1706-1715.
75. Goss, W.; Deitz, W.; Cook, T. Mechanism of action of nalidixic acid on Escherichia coli. II. Inhibition of deoxyribonucleic acid synthesis. J. Bacteriol, 1965; 89: 1068-1074.
76. Engle, E.C.; Manes, S.H.; Drlica, K. Differential effects of antibiotics inhibiting gyrase. J. Bacteriol, 1982; 149: 92-98.
77. Khodursky, A.; Cozzarelli, N. The mechanism of inhibition of topoisomerase IV by quinolone antibacterials. J. Biol. Chem, 1998; 273: 27668-27677.
78. Hiasa, H.; Marians, K.J. Two distinct modes of strand unlinking during theta-type DNA replication. J. Biol. Chem, 1996; 271: 21529-21535.
79. Wentzell, L.; Maxwell, A. The complex of DNA gyrase and quinolone drugs on DNA forms a barrier to the T7 DNA polymerase replication complex. J. Mol. Biol, 2000; 304: 779-791.
80. Krasin, F.; Hutchinson, F. Repair of DNA double-strand breaks in Escherichia coli, which requires recA function and the presence of a duplicate genome. J. Mol. Biol, 1977; 116: 81-98.
81. Chow, R.; Dougherty, T.; Fraimow, H.; Bellin, E.; Miller, M. Association between early inhibition of DNA synthesis and the MICs and MBCs of carboxyquinolone antimicrobial agents for wild-type and mutant [gyrA nfxB(ompF) acrA] Escherichia coli K-12. Antimicrob. Agents Chemother, 1988; 32: 1113-1118.
82. Gootz, T.D. Bactericidal assays for fluoroquinolones. Methods in Mol. Biol, 2001; 95: 185-194.
83. Champoux, J.J.; Been, M.D. Topoisomerases and the swivel problem, in Mechanistic Studies of DNA replication and Genetic recombination: ICN-UCLA Symposia on Molecular and Cellular Biology, B Alberts, Editor, 1980, Academic Press: New York, 809-815.
84. Khodursky, A.B.; Zechiedrich, E.L.; Cozzarelli, N.R. Topoisomerase IV is a target of quinolones in Escherichia coli. Proc. Nat. Acad. Sci. U.S.A, 1995; 92: 11801-11805.
85. Andriole VT. The Quinolones: Past, Present, and Future. Clin Infect Dis, 2005; 41(Supplement 2): S113S119.
86. Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. BMC Infect Dis, 2011; 11: 99.
87. Kotwani A, Chaudhury RR, Holloway K. Antibioticprescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. Value Health, 2012; 15(Supplement 1): S116-9.
88. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol, 2011; 72(3): 381–393.
89. Leone R, Venegoni M, Motola D, Moretti U, Piazzetta V, Cocci A, Resi D, Mozzo F, Velo G, Burzilleri L, Montanaro N, Conforti A. Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. Drug Saf, 2003; 26: 109–20.

90. Domagala JM. Structure-activity and structure-sideeffect relationships for the quinolone antibacterials. J Antimicrob Chemother, 1994; 33(4): 685-706.
91. Thomas RJ. Neurotoxicity of antibacterial therapy. South Med J, 1994; 87(9): 869-74.
92. Owens RC, Ambrose PG. Antimicrobial Safety: Focus on Fluoroquinolones. Clinical Infectious Diseases, 2005; 41: S144–57.
93. Takayama S, Hirohashi M, Kato M, Shimada H. Toxicity of quinolone antimicrobial agents. J Toxicol Environ Health, 1995; 45(1): 1-45.
94. Unseld E, Ziegler G, Gemeinhardt A, Janssen U, Klotz U. Possible interaction of fluoroquinolones with the benzodiazepine-GABAA-receptor complex. Br J Clin Pharmacol, 1990; 30(1): 63-70.
95. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis, 1999; 28(2): 352-64.
96. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. Clin Pharmacokinet, 1988; 14(2): 96-121.
97. Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. Am J Med, 1991; 91(6A): 153S-161S.
98. Janknegt R. Drug interactions with quinolones. J Antimicrob Chemother, 1990; 26: 7-29.
99. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. Drugs Aging, 2010; 27(3): 193-209.
100. De Bleecker JL, Vervaet VL, De Sarro A. Reversible orofacial dyskinesia after ofloxacin treatment. Mov Disord, 2004; 19: 731-2.
101. Pastor P, Motinho E, Elizalde I, Cirera I, Tolosa E. Reversible oro-facial dyskinesia in a patient receiving ciprofloxacin hydrochloride. J Neurol, 1996; 243: 616–7.
102. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. Ann Pharmacother, 1996; 30: 138–41.
103. Moorthy N, Raghavendra N, Venkatarathnamma PN, Levofloxacin-induced acute psychosis. Indian J Psychiatry 2008; 50(1): 57–58.