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Neuropsychological Side Effects Associated with Fluoroquinolone Therapy: A Qualitative Review with Recommendations for Future Research

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Abstract

Fluoroquinolone toxicity can best be described as a cluster of symptoms that appear during or after the administration of a fluoroquinolone antibiotic. Toxicity reactions may be immediate or delayed, acute or persistent, and mild to severe. They may be localized to one bodily system or present with multi-system pathology. The second most common type of adverse effect associated with fluoroquinolone therapy are effects of the central nervous system (CNS), and these CNS effects are likely to take the form of neuropsychological symptoms such as anxiety, insomnia and depression. Although fluoroquinolone-induced CNS toxicity is well documented in the literature, how this toxicity manifests into the presentation of neuropsychological symptoms remains poorly understood.

These reactions are often missed by providers or attributed to other disorders, and patients are denied the opportunity to discontinue fluoroquinolone therapy on time. In addition, reactions may be worsened by the coadministration of NSAIDs or psychotropic drugs. Future research must focus on the prevention of adverse reactions through appropriate prescribing practices and the identification of risk factors associated with toxicity. Research is also needed to determine how to effectively treat fluoroquinolone-induced neuropsychological symptoms that persist beyond discontinuation of the antibiotic.

Keywords*: antibiotics, fluoroquinolones, toxicity, neuropsychological, central nervous system*

Fluoroquinolones are the most commonly prescribed antibiotics in the United States (Linder, Huang, Steinman, Gonzales, & Stafford, 2005). However, over half of the fluoroquinolone antibiotics produced have been withdrawn from the market due to concerns about toxicity (Quinolone Vigilance Foundation [QVF], 2016). Many reports have demonstrated an acceptable safety profile for many of the fluoroquinolones including ciprofloxacin and levofloxacin (Ball, Mandell, Niki, & Tillotson, 1999; Lipsky & Baker, 1999), yet other reports have revealed serious multi-symptom adverse effects that may occur during or after the use of fluoroquinolones (Daneman, Lu, & Redelmeier, 2015; Golomb, Koslik, & Redd, 2015). In addition, patient-led research and adverse event reporting have generated scrutiny surrounding both the safety profile and the prescribing practices associated with this class of antibiotics. In 2015, the FDA formally recognized a constellation of symptoms leading to disability associated with fluoroquinolones and referred to the syndrome as "Fluoroquinolone-Associated Disability" (FQAD) although this term is not a formal diagnosis or legal definition for disability (Food and Drug Administration [FDA], 2015). Previous scientific reports have used the term "fluoroquinolone toxicity" to refer to adverse events experienced as a result of fluoroquinolone use (Golomb et al., 2015; Lipsky & Baker, 1999), and that term will be used for this review.

Fluoroquinolones have been associated with adverse effects in multiple organ systems including the cardiovascular system (Rao et al., 2014), the musculoskeletal system (Daneman et al., 2015; van der Linden, van de Lei, Knob, Knol & Sticker, 1999), the renal system (Barbar, 2013; Kabbara, Ramadan, Rahbany & Al-Natour, 2015), the ocular system (Chui et al., 2014; Walker & Tyler, 2006), and the nervous system (Kandasamy & Srinath, 2012; Galatti et al., 2005; Lode, 1999). Compared to other antibiotics, fluoroquinolones are more likely to produce serious central nervous system (CNS) side effects during or after administration (Galatti et al., 2005; Owens & Ambrose, 2005) Moreover, several studies have found that CNS effects are one of the most common types of adverse events associated with fluoroquinolones (Lipsky & Baker, 1999; Mandell & Tillotson, 2002), and may include

neuropsychological symptoms such as insomnia, anxiety, depression, and psychosis (Fish, 2001; Lode, 1999; Owens & Abrose, 2005). Effects of the peripheral nervous system (PNS) may also commonly appear in conjunction with CNS effects and present as neuropsychological.

Although the CNS toxicity of fluoroquinolones is widely recognized in the literature, research has indicated that physicians often fail to recognize neuropsychological symptoms as being associated with fluoroquinolone use (Cohen, 2001). The frequency of these reactions are likely underestimated (Grill & Manganti, 2011). The cluster of symptoms associated with fluoroquinolone toxicity (specifically the neuropsychological symptoms) may present confusingly, and these medication-induced symptoms may seem indistinguishable from true psychiatric disorders. This may be particularly problematic because fluoroquinolones are known to react poorly with many psychotropic drugs (Kennedy, Jann & Kutsher, 2013; McConnell, 2008) and fluoroquinolone toxicity may continue well beyond discontinuation of the antibiotic (Golomb et al. 2015). The purpose of the current review is to provide an overview of fluoroquinolone toxicity with neuropsychological symptoms to promote awareness of these complex and devastating adverse reactions. Better awareness of fluoroquinolone-induced neuropsychological symptoms may result in more rapid discontinuation of the fluoroquinolone antibiotic and the avoidance of inappropriate pharmacological treatment, leading to a better prognosis for the patient. Moreover, awareness of these adverse effects may increase preventative efforts by providers who regularly prescribe fluoroquinolone antibiotics.

Fluoroquinolone Toxicity

Fluoroquinolone toxicity is a term used to describe a cluster of symptoms that arise during or after the use of oral or intravenous fluoroquinolone antibiotics (Golomb et al., 2015; Lipsky & Baker, 1999). Reactions tend to be individualized, that is, each person experiences a unique symptom profile and duration of effects. These adverse reactions can be mild, moderate, or severe (Sepcić et al., 2009), and adverse effects can be experienced after just one dose (McEvoy, 1999). Although many reports suggest that discontinuation of the medication relieves symptoms of toxicity (Sepcić et al. 2009; Yasuda et al., 1999), other reports suggest that the effects of toxicity may continue for months or years, and in some cases may be permanent (FDA, 2105; Golomb et al., 2015). Fluoroquinolone toxicity may affect multiple bodily systems or be localized to just one system. There is currently no evidence-based treatment for fluoroquinolone toxicity, and treatment generally revolves around palliative care (Cohen, 2001). Although individual adverse effects of fluoroquinolones have been largely recognized in the literature, only a handful of studies have acknowledged the severe, multi-system pathology that may occur as a result of fluoroquinolone use. Some of the most under-recognized and poorly understood symptoms within this pathology are neuropsychological symptoms associated with toxicity of the central and peripheral nervous systems (Cohen, 2001).

Central Nervous System (CNS) Effects of Fluoroquinolones

Numerous survey reports and case histories have documented the central nervous system effects of fluoroquinolones in patient populations over the last several decades (Lode, 1999; Galatti, et al., 2005; Golomb, 2015; Slobodin et al., 2008; Tomé & Filipe, 2011), yet most of these effects remain largely unknown to providers (Cohen, 2001). Some of the more commonly reported central nervous system effects of fluoroquinolones are headache and dizziness, and these symptoms are likely to resolve after discontinuation of antibiotics (Sousa, Alves, Fortuna, & Falcão, 2014). More severe central nervous system effects include seizures (Bellon, Perez-Garcia, Coverdale, & Chacko, 2009; Gervasoni, 2013; Yasuda et al. 1999) and pseudotumor cerebri (Winrow & Supramaniam, 1990), which may take longer to subside or require immediate medical interventions. It is important to note that many of the central nervous system effects appear in the form of neuropsychological symptoms and may be harder to attribute to the administration of an antibiotic. In one study of patients who experienced an adverse reaction to fluoroquinolones, 78% of them experienced central nervous system effects, including neuropsychological symptoms such as anxiety, insomnia, disorientation, depersonalization, depression, confusion and hallucinations. In addition, 80% of patients in the study described their symptoms as severe and 71% of patients stated their symptoms have lasted more than a year at the time of data collection (Cohen, 2001). Numerous case studies also describe instances of fluoroquinolone-induced insomnia (Bowie, Willetts, & Jewesson, 1989; Kandasamy & Srinath, 2012), anxiety (Kandasamy & Srinath, 2012), and psychosis (Grimm & Alm, 2007; Moorthy, Raghavendra, & Venkatarathnamma, 2008; Slobodin, et al., 2009), with accompanying impairments to cognition, memory and judgment. Patients experiencing these symptoms are often referred to psychiatric care, and the true cause of their symptoms may subsequently go undetected. Unfortunately, patients may also be told by the prescribing provider to continue taking the antibiotic despite their complaints of neuropsychological adverse effects (Cohen, 2001).

Peripheral nervous system (PNS) effects of Fluoroquinolones

Fewer studies have focused on the PNS effects of fluoroquinolones, which take the form of sensory and motor disturbances mostly affecting the limbs and head (Ali, 2014; Cohen, 2001). Patients with fluoroquinolone-induced neuropathy often report feelings of buzzing, tingling, numbness, burning pain, shooting pain, electric shocks or crawling sensations on the skin. Peripheral nervous system motor disturbances may include weakness, impaired coordination, fasciculations, spasms, tremors or myoclonus. In the same study of patients with fluoroquinolone-induced side effects (cited above), 91% reported PNS sensory symptoms and 55% reported PNS motor symptoms. Although this study had limitations that included small sample size and the use of convenience sampling, other studies have confirmed the link between fluoroquinolones and peripheral nervous system effects (Ali, 2014;

Hedenmalm & Spigset, 1996). These PNS effects may present as neuropsychological (e.g., somatic symptom disorder) or worsen existing neuropsychological symptoms. Therefore, these PNS effects may limit functioning, cause severe disability, and contribute to a worsening of depression, anxiety and insomnia caused by fluoroquinolones.

Mechanisms of Action

Both the structure and the mechanism of action of fluoroquinolones make them extremely potent antimicrobial agents. Fluoroquinolones inhibit bacterial gyrase, an enzyme involved in DNA replication, recombination and repair, to stop bacterial growth (Maxwell, 1992).

The features that enhance the bactericidal effects of fluoroquinolones may also be the features that are most implicated in causing adverse side effects (Domagala, 1994). For example, the addition of a fluorine atom at the C8 position from an older quinolone structure has enhanced the spectra of antimicrobial activity and may be responsible for increased tissue concentrations (DeSarro & DeSarro, 2001). Several studies have shown that fluoroquinolones extensively penetrate brain tissue and appear in concentrations greater or equal to that of serum concentrations (Davey, et al., 1994; IIgin, et al., 2015; Leone et al., 2002). Several mechanisms of action have been proposed for how fluoroquinolone antibiotics cause neuropsychological symptoms once in the brain, most of which focus on changes in neurotransmitters and increased oxidative stress.

CNS Excitation through GABAA Binding

Fluoroquinolones may induce central nervous system effects through direct excitatory action or the coadministration of other pharmacological agents (Lode, 1999). Studies have demonstrated that fluoroquinolones can cause nervous system excitation through fluoroquinolone binding at the GABAA receptor thereby blocking the natural ligand (Green & Halliwell, 1997; Halliwell, Davey, & Lambert, 1993). Specifically, animal models have shown that fluoroquinolones may cause epileptogenic activity through the substituent at the C7 position leading to a lower inhibition of GABA binding (Akahane, Sekiguchi, Une & Osada, 1989). It is important to note that coadministration with NSAIDs may potentiate the antagonistic action of fluoroquinolones at GABAA receptors greater than 30,000 times (Halliwell, Davey & Lambert, 1991). Central nervous system excitation through these mechanisms is likely to present as the neuropsychological symptoms of anxiety and insomnia associated with fluoroquinolones (Kandasamy & Srinath, 2012). In addition to changes in GABA activity, rodent studies have indicated that fluoroquinolones may decrease serotonin levels and increase glutamate levels in the

brain, providing additional mechanisms by which these drugs induce neuropsychological symptoms (Abdel-Zaher et al., 2012; Ilgin et al., 2015).

Neurological Toxicity through Oxidative Stress

Fluoroquinolones may create oxidative stress in the brain after administration of therapeutic doses leading to neurological toxicity. In a recent study of rats administered 14 days of 50 mg/kg of ciprofloxacin, the drug produced oxidative stress in the brain through both increases in malondialdehyde levels and decreases in glutathione. These changes occurred along with altered brain neurotransmitter levels (Ilgin et al., 2015). Furthermore, these effects may be accompanied by increases in the expression and activity of brain inducible NO synthase (Abdel-Zaher, 2012).

Fluoroquinolones have also been shown to induce mitochondrial dysfunction through oxidative damage in mammalian cells. In a study by Kalghatigi and colleagues (2013), epithelial cell lines were exposed to clinically relevant doses of ciprofloxacin and showed an increase in intracellular reactive oxygen species (ROS) and mitochondrial dysfunction with subsequent DNA, lipid and protein damage (Kalghat et al., 2013). This study drew attention to the potential long term impact of neurological and neuropsychological symptoms associated with fluoroquinolone toxicity, as several neurodegenerative disorders such as multiple sclerosis and amyotrophic lateral sclerosis have been linked to the dysfunction of mitochondria (Campbell, Worrall, & Mahad, 2014; Paloma & Manfredi, 2014). This may also be the mechanism that explains why some toxicity reactions to fluoroquinolones are delayed and longstanding.

Prescribing Practices of Fluoroquinolone Antibiotics

Fluoroquinolones are one of the most potent antibiotics on the market and are often prescribed for serious life-threatening infections, but they are also commonly prescribed for less serious infections of the urinary tract, upper respiratory tract or sinuses. Research indicates that many prescribed fluoroquinolone regimens may be unnecessary or misused (Lautenbach et al., 2003; Werner, Hecker, Sethi, & Donseky, 2011). The use of fluoroquinolones has been associated with nosocomial infections such as Staphylococcus aureus (MRSA) and Clostridium difficile (Leblanc et al., 2006; Owens, Donskey, Gaynes, Loo, & Muto, 2008) and concerns regarding increased antibiotic resistance to fluoroquinolones has generated attention (De Lastours & Fantin, 2015; Neuhauser et al., 2003). The extent and spectrum of adverse reactions to fluoroquinolone antibiotics, including neuropsychological symptoms, is concerning and has led many physicians and scientists to question the guidelines surrounding the

prescribing of these drugs for conditions that are not immediately life-threatening (Sepcić et al., 2009; FDA, 2015).

Considerations for the Prevention of Fluoroquinolone Toxicity

Appropriate prescribing practices which focus on the utilization of fluoroquinolones for severe life-threatening infections may be the best way to reduce the incidence of fluoroquinolone toxicity in patients. Although many individual side effects are well documented in fluoroquinolone labeling, multi-system adverse reactions are not described. Furthermore, the description of central nervous effects in the warning labels varies among specific drugs in the fluoroquinolone class. Although it is generally thought that warning labels serve as adequate informed consent for patients, it may be unrealistic to expect them to understand the seriousness of the side effect profile associated with fluoroquinolones. Additional verbal informed consent and adequate explanations of possible side effects by physicians and pharmacists may mitigate adverse effects through faster recognition of symptoms. Rapid discontinuation of the drug may lead to a better prognosis in some cases (Sepcić et al. 2009; Yasuda et al., 1999). Patient and provider awareness of common drug interactions with fluoroquinolones is another way to avoid neurological toxicity leading to CNS and PNS adverse effects. Many infections that fluoroquinolones are prescribed to treat involve pain and inflammation and NSIADs may inadvertently be coadministered with the fluoroquinolone, leading to a drastic increase in the risk for the central nervous system toxicity (Fish, 2001; Halliwell, Davey & Lambert, 1991).

Post marketing surveillance of fluoroquinolone related-adverse events must be made a priority. There are numerous possibilities as to why these events continue to go unrecognized by physicians despite documentation in the scientific literature. First, the nature of adverse events may present confusingly and the symptoms may mimic those of other diseases or disorders. Neuropsychological symptoms that are medication-induced may behave quite similarly to psychological disorders that are not-medication induced. This may be especially true for anxiety, depression and insomnia. Secondly, fluoroquinolone adverse events may be delayed and appear after the discontinuation of the drug (Golomb et al., 2015; FDA, 2015), which may prohibit both patients and physicians from making the connection between the drug and subsequent neuropsychological symptoms. Lastly, even if the connection between the drug and the subsequent symptoms is made, adverse event reporting still may not occur. Patients may be unaware that they can report these events to the FDA, and physicians may not be inclined to report the events themselves (QVF, 2016). Therefore, only a fraction of fluoroquinolone-induced neuropsychological adverse events may be reported the Federal Adverse Event Reporting System (FAERS), giving providers an incomplete picture of how common these events are.

Considerations for Treatment of Fluoroquinolone Toxicity

Currently, there is no evidence-based treatment for fluoroquinolone toxicity (Cohen, 2001). Symptoms of fluoroquinolone toxicity involving the CNS and PNS, specifically the neuropsychological symptoms, may not respond to traditional pharmacological treatments for psychological disorders. For example, the results for benzodiazepine therapy as a potential treatment for the neuropsychological symptoms of fluoroquinolone toxicity are understudied. Because fluoroquinolones compete for the benzodiazepine receptor site, they may alleviate symptoms of CNS toxicity in healthy patients (Unseld, Ziegler, Gemeinhardt, Janssen, & Klotz, 2012). However, benzodiazepines may not be helpful for those whose reactions were precipitated by the use of NSAIDs, or for patients currently being treated with benzodiazepines for other disorders. For patients that currently use benzodiazepines, administration of fluoroquinolones may precipitate withdrawal (McConell, 2008). Antipsychotic drugs used for the treatment of insomnia or psychosis may also interact with fluoroquinolones (Kennedy et al., 2013). Moreover, cognitive-behavioral therapies may also fail to show benefit for patients who are experiencing extreme biological reactivity of the autonomic nervous system that has been medication-induced, especially for patients with symptoms that persist well beyond the discontinuation of the drug. There are very few treatment options that may alleviate the neuropsychological symptoms of fluoroquinolone toxicity, which should bolster the argument that increased awareness and prevention are of vital importance.

Recommendations for Future Research

Future research must focus on the prevention of fluoroquinolone toxicity. Given the fact that fluoroquinolones are very useful in treating serious bacterial infections, complete discontinuation of this class of drugs is unlikely. Therefore, the discovery of mechanisms that may prevent toxicity is needed. For instance, some promising research has demonstrated that the coadministration of *N*-acetyl-l-cysteine (NAC) may reduce the incidence of ROS-mediated damage in cells without disrupting the bactericidal properties of fluoroquinolones (Kalghatgi et al., 2013). Future investigations must also focus on how to properly identify fluoroquinolone-induced neuropsychological symptoms and how to distinguish these symptoms from non-medication-induced psychological symptoms. Greater awareness of the delayed nature of reactions should also be a target of educational efforts. As previously mentioned, faster diagnosis can lead to more rapid discontinuation of the offending drug and avoidance of medications that could exacerbate symptoms. Given the vast number of people that may be suffering from fluoroquinolone toxicity, more research is needed to identify risk factors that may be associated with adverse reactions.

Conclusions

Many experimental studies have documented the CNS toxicity of fluoroquinolones, yet very few studies have focused on how to adequately recognize or treat the neuropsychological symptoms that may manifest as a result of this toxicity. Neuropsychological symptoms induced by fluoroquinolones may significantly impair functioning and may contribute to permanent disability. Greater consideration must be given to preventative efforts including responsible prescribing and informed consent. Treatment considerations should include the unique nature of each adverse reaction, with an understanding that discontinuation of fluoroquinolone therapy may not completely resolve symptoms. Providers must be careful to avoid drug interactions during fluoroquinolone therapy that may precipitate or exacerbate neurotoxic reactions. Awareness efforts should not only target prescribing providers but should also include clinical mental health providers, as they may be on the front lines of identifying persistent fluoroquinolone-induced neuropsychological symptoms. More research is needed to gain a better understanding of who may be at risk for a fluoroquinolone reaction to prevent serious and persistent neuropsychological adverse events.

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