References for FQ-Induced Neurological Symptoms, implicating NMDA/GABA receptors and MG/ACh mechanisms.

The Fluoroquinolone antibiotics have a long history of either causing, or possibly "unmasking" CNS, PNS, and MG-related (Myasthenia Gravis/ACh) symptoms as part of their adverse profile. This is in addition to the tendinitis, tendinopathies, and tendon ruptures they can cause.

The FDA required an update on all drug labels and Medication Guides as of 8/15/13 to warn of the risk for permanent Peripheral Neuropathy:

http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection (8/15/13 update). *"The U.S. Food and Drug Administration (FDA) has required the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of peripheral neuropathy. This serious nerve damage potentially caused by fluoroquinolones (see Table for a list) may occur soon after these drugs are taken and may be permanent."*

Additionally, the FDA required an updated similar warning regarding Myasthenia Gravis in February 2011:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm247115.htm Risk of fluoroquinolone-associated Myasthenia Gravis Exacerbation February 2011 Label Changes for Fluoroquinolones. New safety information should be included in the labeling for fluoroquinolone products. *"Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis."*

The FDA required warning of possible tendon problems and ruptures in July 2008:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126085.htm *"FDA is notifying the makers of fluoroquinolone antimicrobial drugs for systemic use of the need to add a boxed warning to the prescribing information about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones and to develop a Medication Guide for patients."*

FQ-Induced CNS/Encephalopathy symptoms implicating NMDA-R and GABA-R:

http://www.ncbi.nlm.nih.gov/pubmed/12052667 Clinical toxicological aspects of fluoroquinolones. *"Pathogenesis of the neurotoxic effects of fluoroquinolones could be related to the activation of the NMDA receptor."*

http://www.ncbi.nlm.nih.gov/pubmed/10456380 Potential interactions of the extended-spectrum fluoroquinolones with the CNS. *"Inhibition of brain gamma-aminobutyric acid (GABA) receptor binding appears to be a strong indicator of CNS activity, though N-methyl-D-aspartate receptor binding has also been implicated."*

http://www.ncbi.nlm.nih.gov/pubmed/9132619 Psychopathological syndromes in treatment with gyrase inhibitors. *"Psychopathological and neurological adverse drug reactions (ADR) have been repeatedly reported during treatment with gyrase inhibitors (fluorquinolones)."*

http://www.ncbi.nlm.nih.gov/pubmed/7902066 Involvement of inhibitory and excitatory neurotransmitters in levofloxacin- and ciprofloxacin-induced convulsions in mice. *" . . . convulsions induced by these quinolones alone and by these quinolones administered with BPAA may be mediated largely through glutamate and GABA(B) rather than GABA(A) receptors in mice."*

http://www.ncbi.nlm.nih.gov/pubmed/17478598 A case of ciprofloxacin-induced acute polymorphic psychosis with a distinct deficit in executive functions. "*Comparing the psychopharmacological features of ketamine and ciprofloxacine we hypothesize that ciprofloxacine leads to psychosis similar to a ketamine induced psychosis . . . we were the first in obtaining a detailed neuropsychological testing . . . from a more psychopharmacological point we hypothesize that the ciprofloxacine-induced psychosis shares aspects with an NMDA-antagonist induced psychosis . . . ciprofloxacine shows inhibiting properties at the GABAa-receptor and leads to an up regulation of glutamatergic neurotransmission. Other drugs, which act via up regulation of glutamatergic neurotransmission, are NMDA-antagonists like ketamine or phenycyclidine, which cause a so-called model-psychosis . . . Second, a recent fMRI study in healthy probands showed that ketamine induces a distinct deficit of the prefrontal cortex (Honey et al. 1203-14) , a deficit with parallels to the one seen in our patient. As a consequence of this, we hypothesize that ciprofloxacine induced a deficit in prefrontal mediated executive functions via enhanced glutamate neurotransmission. Our case is a clinical hint for the hypothesis that ciprofloxacine gains its psychosis-inducing properties via a glutamate-induced disruption of frontal executive functions. From a clinical point of view it highlights the need of a better understanding of the central nervous side effects ofcommon used antibiotics."*

http://www.ncbi.nlm.nih.gov/pubmed/1504404 Ciprofloxacin-induced psychosis.

http://www.ncbi.nlm.nih.gov/pubmed/23616064 Levofloxacin-induced seizures in a patient without predisposing risk factors: the impact of pharmacogenetics.

http://www.ncbi.nlm.nih.gov/pubmed/1647389 The effects of quinolones and NSAIDs upon GABA-evoked currents recorded from rat dorsal root ganglion neurones.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC105691/ Determination of the Excitatory Potencies of Fluoroquinolones in the Central Nervous System by an In Vitro Model *"Fluoroquinolones have been reported to induce central nervous system side effects, including seizures and psychiatric events . . . These investigations pointed to the N-methyl-D-aspartate receptor as the probable target of the fluoroquinolone effects"*.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4202555/ The Effect of Ciprofloxacin Injection on Genetically Absence Prone (Wag/Rij) Rat's Electroencephalogram Characteristics. *"These results may be due to involvement of GABA antagonistic effects of FQs and/or Mg2+ linked blockade of NMDA receptors."*

http://www.ncbi.nlm.nih.gov/pubmed/17046250 Microwave prompted multigram synthesis, structural determination, and photo-antiproliferative activity of fluorinated 4-hydroxyquinolinones. *"3-Unsubstituted 4-hydroxyquinolin-2(1H)-one containing F and CF(3) substituent in ring is important pharmacological and synthetic target and basic synthones for a number of antibacterial fluoroquinolones and is promising potent and selective glycine site NMDA receptors."*

http://www.ncbi.nlm.nih.gov/pubmed/9347323 Role of nitric oxide in the convulsive seizures induced by fluoroquinolones coadministered with 4-biphenyl acetic acid. *"These findings suggest that FQs + BPAA exert convulsions by activating NOS partly through the mediation of the NMDA receptor in the brain cells."*

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC172741/ Structure-Epileptogenicity Relationship of Quinolones with Special Reference to Their Interaction with -γ-Aminobutyric Acid Receptor Sites. *"These results indicate that the epileptogenic activity of quinolones possibly relates to the GABA-like structures of substituents at their 7 positions, which act as antagonists of GABA receptors."*

http://www.ncbi.nlm.nih.gov/pubmed/9266796 Inhibitory effect of new quinolones on GABA(A) receptor-mediated response and its potentiation with felbinac in Xenopus oocytes injected with mouse-brain mRNA: correlation with convulsive potency in vivo. *"These findings suggested that the blockade of GABA-ersic neurotransmission in CNS is a dominant mechanism of convulsion induced by NQs and that the convulsant-adverse reaction of NQs in vivo may be predicted from the inhibitory effect on the GABA(A) receptor in vitro using the Xenopus oocytes translation system of exogenous mRNA"*

http://www.ncbi.nlm.nih.gov/pubmed/9021202 Effects of some excitatory amino acid antagonists and drugs enhancing gamma-aminobutyric acid neurotransmission on pefloxacin-induced seizures in DBA/2 mice.

http://www.ncbi.nlm.nih.gov/pubmed/8788959 A patch clamp study of the effects of ciprofloxacin and biphenyl acetic acid on rat hippocampal neurone GABAA and ionotropic glutamate receptors.

http://www.ncbi.nlm.nih.gov/pubmed/24259701 SIADH associated with ciprofloxacin. *"The likely mechanism of this reaction is ciprofloxacin crossing the blood-brain barrier and stimulating the γ-aminobutyric acid and N-methyl-D-aspartate receptors, which leads to the synthesis and release of antidiuretic hormone."*

http://www.ncbi.nlm.nih.gov/pubmed/24259611 Orofacial dyskinesia associated with the use of levofloxacin. *"They are most commonly associated with ciprofloxacin and are thought to be related to inhibition of γ-aminobutyric acid receptors and activation of N-methyl-d-aspartate receptors. Orofacial dyskinesia has previously been reported primarily with second-generation fluoroquinolones, with only a single case report implicating a third-generation fluoroquinolone."*

http://www.ncbi.nlm.nih.gov/pubmed/19430173 Quantitative comparison of the convulsive activity of combinations of twelve fluoroquinolones with five nonsteroidal antiinflammatory agents. *"Concomitant administration of certain fluoroquinolone antimicrobials and nonsteroidal antiinflammatory agents (NSAIDs) induces serious convulsion in humans."*

http://www.ncbi.nlm.nih.gov/pubmed/2771865 Neurochemical studies on quinolone antibiotics: effects on glutamate, GABA and adenosine systems in mammalian CNS.

http://www.ncbi.nlm.nih.gov/pubmed/12367622 Characterization of the interaction between a novel convulsant agent, norbiphen, and GABA(A) and other ligand-gated ion channels. *"A hybrid molecule composed of the antimicrobial, norfloxacin, linked to the non-steroidal anti-inflammatory drug (NSAID), biphenylacetic acid, which we have termed norbiphen, is a lethal convulsant in vivo and an antagonist of rodent GABA(A) receptors in vitro."*

http://www.ncbi.nlm.nih.gov/pubmed/11796360 Convulsant and subconvulsant doses of norfloxacin in the presence and absence of biphenylacetic acid alter extracellular hippocampal glutamate but not gamma-aminobutyric acid levels in conscious rats.

http://www.ncbi.nlm.nih.gov/pubmed/11529690 Biphenylacetic acid enhances the antagonistic action of fluoroquinolones on the GABA(A)-mediated responses of the isolated guinea-pig ileum. *"This suggests that combined administration of fluoroquinolones and biphenylacetic acid synergistically inhibits GABA(A)-receptors at the intestinal level."*

http://www.ncbi.nlm.nih.gov/pubmed/10078039 Encephalopathy induced by fleroxacin in a patient with Machado-Joseph disease.

http://www.ncbi.nlm.nih.gov/pubmed/9351519 Selective antagonism of the GABA(A) receptor by ciprofloxacin and biphenylacetic acid.

http://www.ncbi.nlm.nih.gov/pubmed/9142563 Interaction of ciprofloxacin with diclofenac and paracetamol in relation to it's epileptogenic effect.

FQ-Induced Peripheral Neuropathy

http://www.ncbi.nlm.nih.gov/pubmed/11793615 Peripheral neuropathy associated with fluoroquinolones. *"These cases suggest a possible association between fluoroquinolone antibiotics and severe, long-term adverse effects involving the PNS as well as other organ systems."*

http://www.neurology.org/content/early/2014/08/22/WNL.0000000000000846.short Oral fluoroquinolone use and risk of peripheral neuropathy

http://jac.oxfordjournals.org/content/37/4/831.full.pdf Peripheral sensory disturbances related to treatment with fluoroquinolones

http://hic.sagepub.com/content/2/3/2324709614545225.full.pdf Permanent Peripheral Neuropathy: A Case Report on a Rare but Serious Debilitating Side-Effect of Fluoroquinolone Administration. *"The health risks and side effects of fluoroquinolone use include the risk of tendon rupture and myasthenia gravis exacerbation, and on August 15, 2013, the Food and Drug Administration updated its warning to include the risk of permanent peripheral neuropathy. We present a case of fluoroquinolone-induced peripheral neuropathy in a patient treated for clinically diagnosed urinary tract infection with ciprofloxacin antibiotic."*

http://aop.sagepub.com/content/45/10/1312.extract Hereditary Neuropathy Unmasked by Levofloxacin. "*The molecular genetic analysis revealed the existence of the most common type of hereditary motor and sensory*

neuropathy or Charcot-Marie-Tooth disease" in this previously asymptomatic patient, although the patient's father and only brother revealed mild subclinical (asymptomatic) symptoms upon testing.

http://www.ncbi.nlm.nih.gov/pubmed/15133830 Propriospinal myoclonus after treatment with ciprofloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/11172695 Adverse reactions to fluoroquinolones. an overview on mechanistic aspects.

http://www.ncbi.nlm.nih.gov/pubmed/8835045 Association of a Tourette-like syndrome with ofloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/17357133 Ciprofloxacin Induced Palatal Tremor Palatal tremor

http://www.ncbi.nlm.nih.gov/pubmed/21585220 Quinolones: Review of Psychiatric and Neurological Adverse Reactions.

http://www.ncbi.nlm.nih.gov/pubmed/10832955 Trovafloxacin-induced weakness due to a demyelinating polyneuropathy.

FQ-Induced Myasthenia Gravis

http://www.ncbi.nlm.nih.gov/pubmed/9521283 Fluoroquinolone antibiotics block neuromuscular transmission.

http://www.ncbi.nlm.nih.gov/pubmed/21879778 Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review.

http://www.ncbi.nlm.nih.gov/pubmed/23218195 Levofloxacin-induced myasthenic crisis.

http://www.ncbi.nlm.nih.gov/pubmed/24029473 Fluoroquinolone associated myasthenia gravis exacerbation: clinical analysis of 9 cases.

http://www.ncbi.nlm.nih.gov/pubmed/19232642 Prulifloxacin as a trigger of myasthenia gravis.

http://www.ncbi.nlm.nih.gov/pubmed/16858118 Levofloxacin induced myasthenia crisis.

http://www.ncbi.nlm.nih.gov/pubmed/15259168 Fluoroquinolones should be avoided in myasthenia gravis.

http://www.ncbi.nlm.nih.gov/pubmed/2309517 Exacerbation of myasthenia gravis by norfloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/9017031 Myasthenia gravis and ciprofloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/7481384 Exacerbation of myasthenia gravis by pefloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/8263560 Probable exacerbation of myasthenia gravis by ofloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/2895386 Possible exacerbation of myasthenia gravis by ciprofloxacin.

http://www.ncbi.nlm.nih.gov/pubmed/9932991 Ofloxacin in the Lambert-Eaton myasthenic syndrome.

Glutamate/NMDA and ACh implicated in Tendinopathies

http://www.ncbi.nlm.nih.gov/pubmed/22354721 Glutamate receptors in tendinopathic patients. *"Tendinopathic biopsies exhibited increased occurrence of NMDAR1, phospho-NMDAR1, SP, and mGluR5, while mGluR6-7 were not increased and mGluR1 was not found."*

http://www.ncbi.nlm.nih.gov/pubmed/18050306 VGluT2 expression in painful Achilles and patellar tendinosis: evidence of local glutamate release by tenocytes.

http://www.ncbi.nlm.nih.gov/pubmed/19422642 Coexistence of up-regulated NMDA receptor 1 and glutamate on nerves, vessels and transformed tenocytes in tendinopathy. " *Elevated levels of the neurotransmitter glutamate and the presence of its receptor, N-methyl-d-aspartate receptor type 1 (NMDAR1), have been established in patients with tendinopathy, i.e. chronic tendon pain and degeneration*."

http://www.ncbi.nlm.nih.gov/pubmed/11562137 In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee.

http://www.ncbi.nlm.nih.gov/pubmed/11899264 Chronic tendon pain: no signs of chemical inflammation but high concentrations of the neurotransmitter glutamate. Implications for treatment?

http://www.ncbi.nlm.nih.gov/pubmed/11354854 Glutamate NMDAR1 receptors localised to nerves in human Achilles tendons. Implications for treatment? *"The NMDAR1 immunoreaction was usually confined to acetylcholinesterase-positive structures, implying that the reaction is present in nerves."*

http://www.ncbi.nlm.nih.gov/pubmed/11186404 In vivo investigation of ECRB tendons with microdialysis technique--no signs of inflammation but high amounts of glutamate in tennis elbow.

http://www.ncbi.nlm.nih.gov/pubmed/19139865 Glutamate and capsaicin-induced pain, hyperalgesia and modulatory interactions in human tendon tissue.

http://www.ncbi.nlm.nih.gov/pubmed/16888051 Microarray analysis of the tendinopathic rat supraspinatus tendon: glutamate signaling and its potential role in tendon degeneration.

http://www.ncbi.nlm.nih.gov/pubmed/16514666 Microarray analysis of healing rat Achilles tendon: evidence for glutamate signaling mechanisms and embryonic gene expression in healing tendon tissue. *"Interestingly, there was also evidence of central nervous system-like glutamate-based signaling machinery present in tendon cells, as has recently been shown in bone. This type of signaling mechanism has not previously been shown to exist in tendon."*

http://www.ncbi.nlm.nih.gov/pubmed/15998342 The chronic painful Achilles and patellar tendon: research on basic biology and treatment. *"The neurotransmitter glutamate (a potent modulator of pain in the central nervous*

system) was, for the first time, found in human tendons. Microdialysis showed significantly higher glutamate levels in chronic painful tendinosis (Achilles and patellar) tendons, compared with pain-free normal control tendons."

http://www.ncbi.nlm.nih.gov/pubmed/12712235 Intratendinous glutamate levels and eccentric training in chronic Achilles tendinosis: a prospective study using microdialysis technique.

http://www.ncbi.nlm.nih.gov/pubmed/10639657 In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain.

http://www.ncbi.nlm.nih.gov/pubmed/24872365 Up-regulation of Glutamate in Painful Human Supraspinatus Tendon Tears. *"A significant increase in the expression of glutamate was seen in tendon tears. There were differences in the expression of metabotropic and ionotropic glutamate receptors. Expression changes were also observed for markers of the sensory and autonomic systems."*

http://www.ncbi.nlm.nih.gov/pubmed/23738276 From muscle research to clinical applications: Do glutamate antagonists aid muscle recovery? *"In addition, blocking of NMDA receptors by various substances rescues motoneurons and increases the number of motor units surviving into adulthood. In this way, glutamate receptor blockers may represent a promising therapeutic approach to retain nerve and muscle function during neurodegenerative events."*

http://www.ncbi.nlm.nih.gov/pubmed/24677026 Glucocorticoids induce specific ion-channel-mediated toxicity in human rotator cuff tendon: a mechanism underpinning the ultimately deleterious effect of steroid injection in tendinopathy? "*The increase in the glutamate receptor NMDAR1 after GCI raises concerns about the potential excitotoxic tendon damage that may result from this common treatment*."

http://www.ncbi.nlm.nih.gov/pubmed/23212463 Human tenocytes are stimulated to proliferate by acetylcholine through an EGFR signalling pathway. *"Studies of human patellar and Achilles tendons have shown that primary tendon fibroblasts (tenocytes) not only have the capacity to produce acetylcholine (ACh) but also express muscarinic ACh receptors (mAChRs) through which ACh can exert its effects."*

http://www.ncbi.nlm.nih.gov/pubmed/21808665 Novel information on the non-neuronal cholinergic system in orthopedics provides new possible treatment strategies for inflammatory and degenerative diseases. *"It is now known that not only is there a neuronal cholinergic system but also a non-neuronal cholinergic system in various parts of the body. Therefore, interference with the effects of acetylcholine (ACh) brought about by the local production and release of ACh should also be considered . . . The conditions discussed are painful and degenerative tendon disease (tendinopathy/tendinosis), rheumatoid arthritis, and osteoarthritis."*

http://www.ncbi.nlm.nih.gov/pubmed/19409915 New insight into the non-neuronal cholinergic system via studies on chronically painful tendons and inflammatory situations. "*There is evidence of both acetylcholine (ACh) production and a marked existence of muscarinic (M2) ACh receptors in these situations . . . The new information obtained suggests that this system plays an important functional role in chronically painful tendons and in inflammatory conditions. The findings of such a system in various parts of the body, when taken together, show that not only should the classical neuronal cholinergic system be considered in discussion of the cholinergic influences in the body. Additionally, the production of ACh in local cells in the tissues represents an important extra supply of the transmitter. ACh effects can be obtained whether or not there is a cholinergic innervation in the tissue."*

http://www.ncbi.nlm.nih.gov/pubmed/18621096 Unexpected finding of a marked non-neuronal cholinergic system in human knee joint synovial tissue. *"The cholinergic anti-inflammatory pathway is a newly discovered pathway. Another recent concept is the existence of a non-neuronal cholinergic system that has, so far, been defined for human tendons, intestine, airways and urinary bladder."*

http://www.ncbi.nlm.nih.gov/pubmed/23378267 The plantaris tendon in association with mid-portion Achilles tendinosis: tendinosis-like morphological features and presence of a non-neuronal cholinergic system. *"The tendon cells showed a distinct immunoreaction for the acetylcholine (ACh) -producing enzyme choline acetyltransferase (ChAT). Frequent fibroblasts were found in the loose connective tissue and these cells also showed a marked ChAT immunoreactions."*

http://www.ncbi.nlm.nih.gov/pubmed/17999088 Presence of a non-neuronal cholinergic system and occurrence of up- and down-regulation in expression of M2 muscarinic acetylcholine receptors: new aspects of importance regarding Achilles tendon tendinosis (tendinopathy). *"We have studied pain-free normal Achilles tendons and chronically painful Achilles tendinosis tendons with regard to immunohistochemical expression patterns of the M(2) muscarinic acetylcholine receptor (M(2)R), choline acetyltransferase (ChAT), and vesicular acetylcholine transporter (VAChT)."*

http://www.ncbi.nlm.nih.gov/pubmed/17289083 Extensive expression of markers for acetylcholine synthesis and of M2 receptors in tenocytes in therapy-resistant chronic painful patellar tendon tendinosis - a pilot study. *"Thus, the results of this pilot study suggest that non-neuronal ACh is highly involved in the pathology of therapy-resistant patellar tendinosis."*

http://www.ncbi.nlm.nih.gov/pubmed/16830327 Immunohistochemical and histochemical findings favoring the occurrence of autocrine/paracrine as well as nerve-related cholinergic effects in chronic painful patellar tendon tendinosis. " *It was found that immunoreactions for the M(2) receptor could be detected intracellularly in both blood vessel cells and tenocytes, especially in tendinosis specimens. Furthermore, in the tendinosis specimens, some tenocytes were seen to exhibit immunoreaction for ChAT and VAChT."*