

INCIDENCE OF FLUOROQUINOLONES INDUCED PSYCHOTIC DISORDERS IN PATIENTS ADMITTED TO DEPARTMENT OF MEDICINE IN A GENERAL HOSPITAL SETUPDnyanda V. Korhale¹, Vidyut A. Khandewale², Shrikant B. Deshmukh³, Ashish V. Saboo⁴**HOW TO CITE THIS ARTICLE:**

Dnyanda V. Korhale, Vidyut A. Khandewale, Shrikant B. Deshmukh, Ashish V. Saboo. "Incidence of Fluoroquinolones Induced Psychotic Disorders in Patients Admitted to Department of Medicine in a General Hospital Setup". *Journal of Evolution of Medical and Dental Sciences* 2015; Vol. 4, Issue 86, October 26; Page: 14942-14948, DOI: 10.14260/jemds/2015/2122

ABSTRACT: Toxic psychosis in adults although it is relatively uncommon side-effect in proportion to the large worldwide consumption of the drugs, there has been a number of case reports of Fluoroquinolone-associated psychosis. Our study was first of its kind as no other prospective cohort study on the use of fluoroquinolones and its relation to development of psychosis has yet been carried out. 2007 patients who were prescribed fluoroquinolones were followed for one month for development of any signs of psychosis out of which 22 patients that is 1.11% was found to have fluoroquinolones induced psychosis. We also discuss the possible neurophysiological mechanisms behind fluoroquinolones induced psychosis.

KEYWORDS: Fluoroquinolones, Psychosis, Incidence.

INTRODUCTION: In Stephen Fried's book "Bitter Pills: inside the hazardous world of legal drugs" he describes severe psychiatric manifestations of fluoroquinolones his wife has undergone through. Of course not all people undergoing through antibiotic therapy develop psychiatric manifestations but few people do, it is worth noting that reactions of this type have been previously labeled as Hoigne's syndrome following numerous similar descriptions associated with penicillin use in the 1950's.⁽¹⁾

Fourteen articles (Describing 15 different cases) meeting the inclusion criteria were studied. The primary findings were as follows: a majority (60%) of reported cases were "Highly suggestive" of a potential causal relationship between antibiotic treatment and psychosis, including 3 cases with a recurrence of psychosis after re-challenge with the same antibiotic; 3 different classes of antibiotics were implicated in this association, including fluoroquinolones, penicillins, and trimethoprim-sulfamethoxazole; for most of the reported cases, both the onset and resolution of psychosis occurred within 1 week of initiation and discontinuation of the antibiotic, respectively.⁽²⁾ Fluoroquinolone; this class of drugs shows some interesting psychopharmacological features they have inhibiting properties at the GABA_A-receptor and leads to an up regulation of glutamatergic neurotransmission.⁽³⁾

Other drugs, which act via up regulation of glutamatergic neurotransmission, are NMDA-antagonists like ketamine or phenacyclidine, which cause a so-called model-psychosis.⁽⁴⁾ Toxic psychosis in adults although it is relatively uncommon side-effect in proportion to the large worldwide consumption of the drugs, There have been a number of case reports of Fluoroquinolone-associated psychosis in the literature that have not been systematically reviewed. From a clinical point of view it is essential, the need of a better understanding of the central nervous side effects of this commonly used antibiotics.

Our study will be first of its kind as no other prospective cohort study on the use of fluoroquinolones and its relation to development of psychosis has yet been carried out despite of the large number of cases.

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AIM: To know the incidence of the fluoroquinolones induced psychotic disorders in the patients admitted to department of medicine in a hospital setting.

MATERIALS AND METHODS: Study design: - Prospective cohort study

Study duration: 2 months.

Study Population: Patients admitted to department of Medicine at Dr. PDMMC Amravati during the period of the study.

Sample Size: All the patients who are prescribed fluoroquinolones and admitted to department of Medicine at Dr. PDMMC during the period of the study fulfilling inclusion criteria.

Inclusion criteria: - Patients above age of 18 years admitted to department of Medicine at Dr. PDMMC during the study period, who are prescribed exclusively fluoroquinolones as antimicrobials in oral and / or injectable form at least for three days.

Exclusion Criteria:

1. Patients who are prescribed other antimicrobials along with fluoroquinolones.
2. Patients who discontinue fluoroquinolones in less than three days.
3. Patients who have undergone any surgical procedure in last one month (Prior to study) or are to undergo any surgical procedure.
4. Patients who use or are using psychotropic substances and medications- e.g. opioids, alcohol or any other medication known to cause psychosis other than antibiotics.
5. Patients on atropine, steroid therapy.
6. Patients who require ICU admission.
7. Patients who have been diagnosed with CNS pathology.
8. Patients who have positive psychiatric past history.

Tools for Assessment: - 1. Structured Performa. 2. DSM – 5:- Diagnostic criteria for brief psychotic disorder.

Method of data collection and analysis: - Informed consent was taken from those being included in the study, a structured Performa was applied to the patients on fluoroquinolones; and psychiatric diagnosis was done according to DSM – 5 criteria. Information was collected and analyzed by applying appropriate statistical tests.

OBSERVATION AND RESULTS: This study consisted of 2007 patients which were on fluoroquinolones or took fluoroquinolones for at least 3 days out of which 33 patients left out. These 33 patients were eliminated which left with 1974 patients in this study. The results are presented under following headings.

	Number of Patients	Percentage
Psychotic Disorder	22	1.11%
No Psychotic Disorder	1952	98.89%
Total	1974	100%

Table 1: Distribution of Cases

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Table 1 shows out of 1974 patients taking fluoroquinolones 22(1.11%) of patients had psychosis while 1952 (98.89%) showed no psychotic disorder.

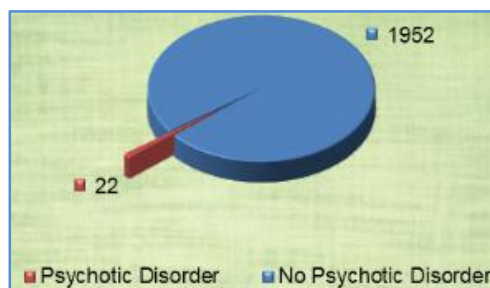


Fig. 1: Distribution of Cases

Age In Years	Psychotic Disorder	No Psychotic Disorder	Total
18 To 28	04(01.45%)	272(98.55%)	276(13.98%)
29 To 38	02(00.78%)	256(99.22%)	258(13.07%)
39 To 48	04(01.10%)	358(98.90%)	362(18.34%)
49 To 58	04(01.06%)	372(98.94%)	376(19.04%)
59 To 68	04(01.27%)	310(98.73%)	314(15.91%)
Above 68	04(01.03%)	384(98.97%)	388(19.66%)
Total	22(01.11%)	1952(98.89%)	1974(100%)

Table 2: Age Wise Distribution

Table 2 shows majority of patients were in Above 68 years (19.66%) and 49 to 58 years (19.04%) of age groups, and psychosis was more common in 18 to 28 years (1.45%) of age group.

Gender	Psychotic Disorder	No Psychotic Disorder	Total
Male	10(00.87%)	1142(99.13%)	1152(58.36%)
Female	12(01.46%)	810(98.54%)	822(41.64%)
Total	22(01.11%)	1952(98.89%)	1974(100%)

Table 3: Gender Wise Distribution

Table 3 shows majority of patients were males 1152 (58.36%), and psychosis was more common in females (1.46%).

Fluoroquinolones	Psychotic Disorder	No Psychotic Disorder	Total
Ofloxacin	08(01.65%)	476(98.35%)	484(24.52%)
Ciprofloxacin	06(01.30%)	456(98.70%)	462(23.41%)
Norfloxacin	04(00.97%)	408(99.03%)	412(20.88%)
Levofloxacin	02(00.70%)	282(99.30%)	284(14.39%)
Lomefloxacin	02(00.72%)	276(99.28%)	278(14.09%)
Moxifloxacin	00(00%)	28(100%)	28(01.40%)
Gemifloxacin	00(00%)	18(100%)	18(00.91%)
Sparfloxacin	00(00%)	08(100%)	08(00.40%)
Total	22(01.11%)	1952(98.89%)	1974(100%)

Table 4: Fluoroquinolones Wise Distribution

p value = 0.89

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Table 4 shows majority of patients were on Ofloxacin 484(24.52%), Ciprofloxacin 462(23.41%) and Norfloxacin 412(20.88%) fluoroquinolones, while psychosis was more common in patients taking Ofloxacin 08(1.65%), Ciprofloxacin 06(1.30%) and Norfloxacin 04(0.97%) fluoroquinolones. The difference in different fluoroquinolones was not statistically significant.

Diagnosis	Incidence Rate
Brief Psychotic Disorder In General Population. ⁽⁵⁾	0.1 to 0.5 %
Fluoroquinolones Induced Psychotic Disorder	1.11%

Table 5: Incidence of Brief Psychotic Disorder in general population Vs Incidence of Fluoroquinolones Induced Psychotic Disorder

p value = 1

Table 5 shows incidence of psychosis was more in patients taking fluoroquinolones than general population.

Days	Number of Patients
Within 7 Days	19(86.36%)
Within 14 Days	02(09.10%)
Within 21 Days	01(04.54%)
Within 28 Days	00(00%)
Total	22(100%)

Table 6: Onset of Fluoroquinolones Induced Psychosis

Table 6 shows out of 22 patients who had fluoroquinolones induced psychosis 19 (86.36%) patients reported psychosis within 7 days after starting fluoroquinolones.

DISCUSSION: As the concept of ‘General Hospital Psychiatry’ or better put ‘consultation liaison psychiatry’ is gaining around, more and more researches focusing on psychiatric aspects of medical diseases are coming forth. This was a prospective cohort study; All the patients who are prescribed fluoroquinolones and admitted to department of Medicine at Dr. PDMMC during the period of the study fulfilling inclusion and exclusion criteria’s were included in this study and consent was taken for the participation in the study. The recruited subjects were divided into eight groups of fluoroquinolones: - Ofloxacin, Ciprofloxacin, Norfloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Gemifloxacin and Sparfloxacin.

All the patients were evaluated using structured Performa and DSM – 5. In this study it was found that incidence of fluoroquinolones induced psychosis was 1.11%. This finding is similar to findings in other studies such as: - Ana M. Tome and Augusto Filipe ⁽⁶⁾ 1.4%; M. Hollweg, H. P. Kapfhammer, M. Krupinski and H.J. Moller ⁽⁷⁾ 0.69%. While the study done by Peter Ball and Glenn Tillotson ⁽⁸⁾ show 0.02 to 0.06% incidence.

The pathophysiological mechanism involved in the development of psychosis is not completely understood. GABA-ergic and monoaminergic mechanisms might play a major part. One contributing factor is the ability of fluoroquinolones to modulate the activity of the gamma-aminobutyric acid (GABA)-A receptor.⁽⁹⁻¹¹⁾ GABA-A receptors, found in the CNS, are most commonly made up of a combination of 5 protein subunits (2-alpha, 2-beta, and 1-gamma).^(12,13)

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When present, the major inhibitory neurotransmitter GABA will bind to the alpha subunit on the GABA-A receptor and allow negatively charged extracellular chloride ions to diffuse into the neuron.^(12,13)

This results in the neuron being slightly hyperpolarized (or have a greater negative resting membrane) and thus being inhibited from some stimulation.^(12,13) Glutamate is the main excitatory neurotransmitter in the CNS and thus has the opposite effect of GABA. Therefore, the CNS maintains a balance between the excitatory and inhibitory activities of the neurons by creating a balance between these two systems.

However, when the binding of GABA to the GABA-A receptor is blocked the neuron may become less polarized (i.e. the threshold for neuronal activation is decreased thereby increasing the risk of that neuron to fire an action potential resulting in the propagation of neuronal impulses in the brain, especially if glutamate is present).

If these neuronal impulses occur at too great a rate or are not coordinated for balanced brain activity within the hippocampus and cortex regions of the brain, then increased CNS stimulation can occur. Fluoroquinolones are known to modulate the biologic activity of these two CNS controls.⁽⁹⁻¹¹⁾ As it relates to the influence of GABA-A receptor activity, the fluoroquinolones are known to non-competitively inhibit the activity of the neurotransmitter, GABA, thus decreasing the activation threshold needed for that neuron to generate an impulse.⁽⁹⁾

It does appear that each of the fluoroquinolone antibiotics do this to a different degree with ofloxacin and levofloxacin being the least likely and norfloxacin, enoxacin and ciprofloxacin being more likely to inhibit GABA-A receptor function.⁽⁹⁾ Other mechanisms have been proposed, such as the involvement of the dopamine receptor and the agonist effect of fluoroquinolones on the glutamate receptor NMDA.⁽⁶⁾ Fluoroquinolones are thought to activate NMDA channels by chelating with magnesium and removing its channel blocking effect.⁽⁶⁾

In our study fluoroquinolones induced psychosis patients were more reported in adults 18(81.82%) patients than elderly (Above 68 years) 4(18.18%) patients. While slightly higher number of patients were reported in females 12(54.54%) than males 10(45.46%). These findings were similar to the study done by Ana M. Tome and Augusto Filipe.⁽⁶⁾ In our study Ofloxacin (1.65%), Ciprofloxacin (1.30%) and Norfloxacin (0.97%) reported more psychosis cases than other fluoroquinolones. We found total 22 cases of fluoroquinolones induced psychosis of which majority 8(36.36%) patients were of ofloxacin induced psychosis then ciprofloxacin induced psychosis 6(27.26%) and 4(18.18%) were of Norfloxacin induced psychosis.

Though this difference was found clinically not significant. In our study we took patients taking 8 different types of fluoroquinolones but the number of patients who took Moxifloxacin, Gemifloxacin and Sparfloxacin were very few 28, 18, 8 patients respectively. So, it's very difficult to comment on these fluoroquinolones. The William R. Keller.⁽⁵⁾ found 0.1 to 0.5% incidence of brief psychotic disorder in general population and in our study the incidence of fluoroquinolones induced psychosis was 1.11% which is high as compare to incidence of brief psychotic disorder in general population. In this study we found that majority of the fluoroquinolones induced psychosis patients 19(86.36%) reported psychosis within 7 days.

The study done by Ana M. Tome and Augusto Filipe.⁽⁶⁾ found onset CNS adverse reaction due to quinolones within few days. While Jay S Cohen.⁽¹⁴⁾ found onset of CNS adverse reaction associated with fluoroquinolones were 15(33%) events beginning within 24 hours of initiating treatment, 26(58%) within 72 hours, and 38(84%) within one week.

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CONCLUSION: The observation and result of our findings shows that fluoroquinolones induces psychosis in 22(1.11%) patients out of 1974 patients on fluoroquinolones, in particularly for Ofloxacin, Ciprofloxacin and Norfloxacin. Several factors should be taken into account when explaining fluoroquinolones induced psychosis, such as CNS penetration and chemical structure of the fluoroquinolones.

LIMITATIONS: Small sample size to accurately apply the results to the community.

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