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Extent of use of QT interval prolonging drugs in psychiatry: A pilot study

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Abstract

A number of drugs are capable of prolonging the QT interval either alone or in combination. Excessive prolonging of QT interval could lead to a potential life threatening fatal abnormal rhytm called Torsades de Pointes. Many antipsychotics drugs were found to have a detrimental effect on the QT interval. The increase in the incidence of sudden cardiac death has been found to be related to the antipsychotic treatment. Many patients taking these drugs mostly psychiatric patients posed to be at a greater risk of developing sudden cardiac death or TdP. Hence, clinicians prescribing these drugs to patients must be alert and aware of the dangerous effect these drugs have on the patients and if possible, to avoid prescribing drugs having with risk of developing QT interval prolonging effect as far as possible.

Keywords: QT prolonging drugs; Torsades de Pointes; QT drug-drug interaction; Psychiatry

1 Introduction

Several drugs can cause prolongation of the QT interval, alone or in combination, and is associated with the abnormal rhythm, Torsades de Pointes (TdP) which is fatal [1-3]. Non cardiac drugs can also have an effect on the QT prolongation and some were reported to cause sudden cardiac death [4, 5]. Many of these drugs have been withdrawn from the market due to the increased incidence of fatal polymorphic ventricular tachycardia [6, 7]. Drug-induced QT-interval prolongation is most often due to a dose dependent inhibition of the cellular inward potassium rectifier (Ikr) current through channels coded by the hERG gene [8-9]. Blockage of the IKr channel, a critical current in the phase 3 repolarization of the cardiac action potential and delayed ventricular repolarisation will lead to early after-depolarisations, which can result in re-entrant pathways or focal activity and TdP [6]. Drug interactions can further increase TdP risk, either by a pharmacodynamic (additive effect of two or more QT-prolonging drugs) or a pharmacokinetic interaction (reducing the metabolism of a QT-prolonging drug by inhibiting cytochrome P-450 enzyme) [10].

Psychiatric patients can be considered a population at risk for drug-induced TdP, because many antipsychotic and antidepressant agents are associated with QT-prolongation [10-15]. Ray *et al.* (2009), showed two-fold increase in sudden cardiac death (SCD) who are currently on treatment of antipsychotics and Weeke*et al.* (2012) found that treatment with certain anti-depressants was associated with up to a 5- to 6-fold increase in the incidence of out-of-hospital cardiac arrest [11,12]. The increased risk of QT-prolongation in psychiatric patients is also due to the use of combinations of psychotropic drugs [16, 17]. In a German conducted in 2010, 45% of 1,014 depressed inpatients received a co-medication with an antipsychotic drug [18]. Sala *et al.* (2005) showed a significant QT-prolongation following the combination of an antipsychotic with an antidepressant agent than monotherapy with the antipsychotic

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agent [17]. Haloperidol, chlorpro-mazine, trifluoperazine, pericycline, prochlorperazine,and fluphenazine are incriminated, but thioridazine may be the worst [19]. Haloperidol and chlorpromazine have a higher VA/SCD risk than olanzapine, risperidone a similar risk and quetiapine a 30 % lower risk than olanzapine. Tricyclic antidepressants are associated with QT-prolongation, especially amitriptyline [20, 21]. Amitriptyline, doxepin, desipramine, imi-pramine, and clomipramine have all been associated with QT prolongation and sudden death has been reported with desipramine, clomipramine, or imi-pramine [22].

Today, literatures have shown that drug-induced QT prolongation and TdP are prevalent in clinical studies. Therefore, physicians treating patients with psychotropic drugs are to be aware of the dangers of life threatening left ventricular arrhythmias. The drugs with high risks tendency to produce QT- prolongation should be avoided as far as practicable [23].

To the best of our knowledge, there is sparse data and very few studies have analyzed the drug induced QT prolongation in psychiatry especially in developing country particularly in India. The aim of our pilot study was to explore the extent of use of QT prolonging drugs in psychiatric patients in a tertiary care hospital. This article was previously presented as an abstract at the EACPT-2022 held at Athens, Greece from 25-27 June 2022.

2 Methods

This study was conducted as a pilot study between May-October 2018 at the Psychiatry Department, NEIGRIHMS, Shillong, India. Following data were collected from case record forms and medical records of the patients: gender, age, diagnosis and details of all prescribed medications.

2.1 Ethical approval

Ethics approval for the study was granted by Institute Ethics Committee (IEC), NEIGRIHMS, Shillong, India (NEIGR/RCELL/2016/0060; Dated 21st November 2016).

2.2 Data analysis

The drugs carrying risk of QTc interval prolongation were explored via the AZCERT QT drugs lists and were categorized on the basis of their TdP risks. QT prolonging drugs were classified in to three risk categories such as; drugs with known risk of TdP are categorized in list-1, while drugs with possible risk of TdP in list-2 and drugs with conditional risk of TdP are included in list-3. The QT prolonging drugs were coded in accordance with the World health Organization (WHO) Anatomical Therapeutic Chemical classification (ATC) index [24 - 26].

2.3 Statistical analysis

Descriptive statistics were used to compute patients' demographics and characteristics of drug interactions. Categorical data were presented as frequencies and percentages.

3 Results

Total 246 patients were included in this study, of which 149 (61%) were males and 97 (39%) were females. Majority of the patients were in the age range 19-39 years (54%) [Table 1].

Average numbers of prescribed medications were 2.74, while in 17% of the cases, ≥5 drugs were prescribed.

The most frequent diagnosis were Depressive disorders (21.5%), Schizophrenia spectrum and other psychotic disorders (17%), Anxiety disorders (15.5%), Sleep-wake disorders (13.5%), Somatic symptoms and related disorders (8.1%), and Bipolar and related disorders (6.5%) [Table 2].

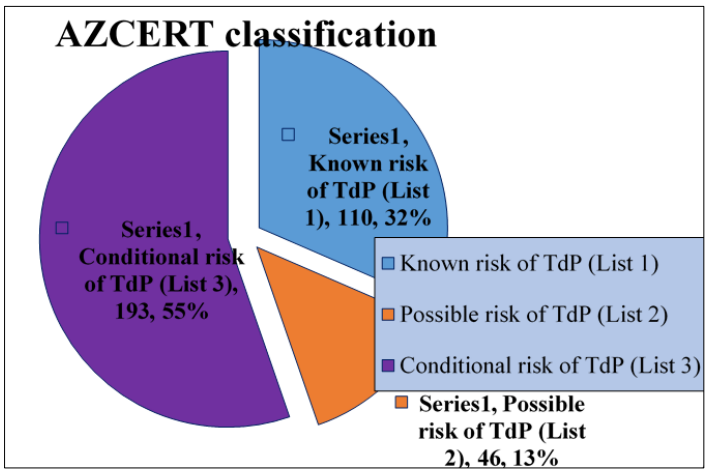
Of the total 246 patients, 207 patients (84.1%) were identified as receiving interacting medication with the ability to induce Tdp and 138 interacting medication pairs with torsanogenic risk were encountered. In accordance with the AZCERT classification of QT prolonging medications, 110(31.5%) of the interacting medications were associated with known risk of TdP, 46(13.2%) interacting medications were associated with possible risk of TdP and 193(55.3%) interacting medications were associated with conditional risk of TdP [Figure 1].

Table 1 Patients' demographics

Variables	Patients: n (%)
Gender	
Male	149 (61)
Female	97 (39)
Age categories	
≤18 yrs	27 (11)
19–39	133 (54)
40–59	71 (29)
>60	15 (6)

Table 2 Major diagnosis identified; DSM5 (American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.)

Variables	Patients: n (%)
Depressive disorders	53 (21.5)
Schizophrenia spectrum and other psychotic disorders	42 (17)
Anxiety disorders	38 (15.5)
Sleep-wake disorders	33 (13.5)
Somatic symptom and related disorders	20 (8.1)
Bipolar and related disorders	16 (6.5)
Obsessive-compulsive and related disorders	9 (3.6)
Neurodevelopmental disorders	8 (3.2)
Substance-related and addictive disorders	7 (2.9)
Neurocognitive disorders	6 (2.5)
Sexual dysfunctions	5 (2)



TdP: Torsades de pointes. TdP risk was based on AZCERT QT drugs lists.

Figure 1AZCERT classification of QT prolonging drugs

According to the therapeutic classification of the drugs, the most frequently interacting medication was from Antidepressants 190 (54.4%), Antipsychotics 135(38.7%), Antidementia 14(4%) and Proton pump inhibitors 7(2%). Total 137 QT-DDIs were identified and percentages calculated in number of all interacting drugs i.e., 348 [Figure 2].

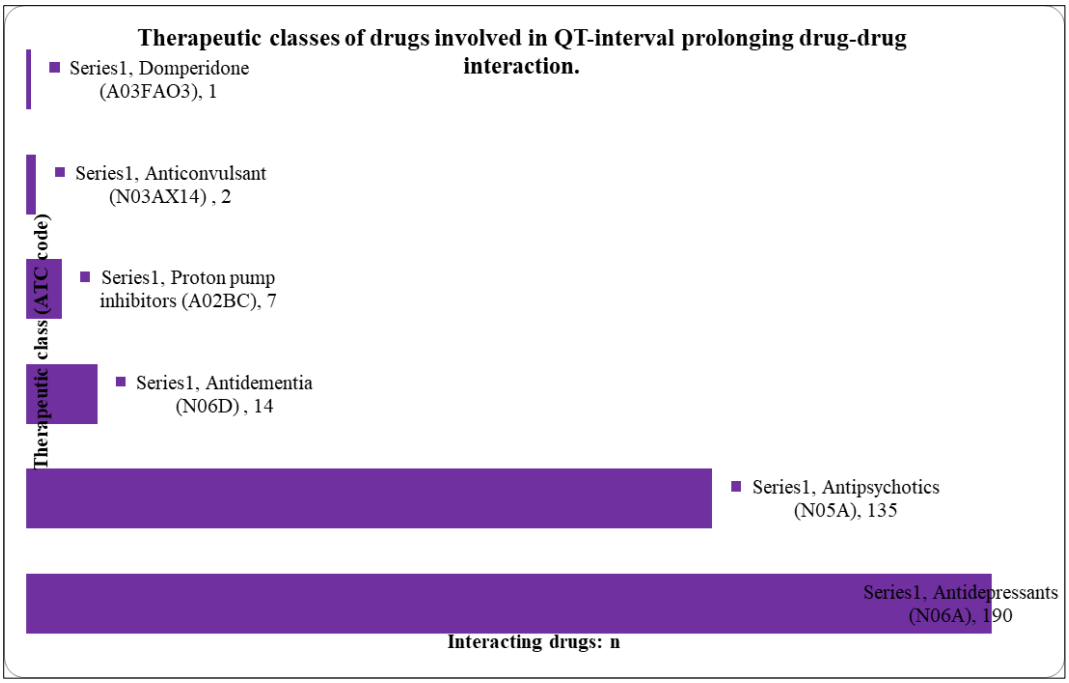


Figure 2 Therapeutic classes of drugs involved in QT-interval prolonging drug-drug interaction

4 Discussions

Very few studies have explored the extent of prescribing of QT prolonging drugs with the ability to induce TdP as well as their combination in the clinical practice. In our present study, we found that 58% and 42% patient were exposed to one and more than one QT prolonging psychotropic drugs respectively. It is quite similar to the recent study conducted in North Jordan where they found 62.3% and 37.7% elderly patient were taking one and more than one QT prolonging drugs respectively [27]. Another study at Pakistan reported that 51.7% patients were exposed to interacting drugs with the ability to induce Tdp [28].

In our study, 54% patient reporting to Psychiatry department was 19-39 yrs similar to earlier study by Biswadeep*et al.* (2019), where the number of young adult patient getting psychiatry care were higher in some of the developing countries [29]. Several drugs used in the treatment of mental diseases are associated with an increased risk of SCD, and therefore, the risk need to be taken into consideration in daily clinical practice. The increased risk of QT-prolongation in psychiatric patients is also due to the use of combinations of psychotropic drugs. Most QT prolonging DDI consisted of combination of antipsychotic and antidepressant which may result in marked QT prolongation and TdP [16, 17]. Patients suffering from psychiatric diseases such as schizophrenia, depression, or bipolar disorders, a treatment associated risk of SCD may be considered to be unavoidable [3] but all possible precautions to reduce the cardiac risk should be taken, including administering the lowest effective dose, optimization of the treatment of co-morbidities, if possible discontinuation or reduction of dosages of negatively interacting drugs, reduction of the administration of undocumented combination regimens to a minimum—and establishing a prudent follow-up for detection of side effects in time.

5 Conclusion

In the present study, a substantial number of patients in Psychiatry are exposing to QT prolonging drugs & drug combinations. Persistent effort should be made to the assessment of QT interval and selection of medication in patients with mental disorders in order to ensure patient safety and prevent life threatening cardiac arrhythmias. ECG monitoring is a useful method to alert clinicians, the possibility of QTc interval prolongation with Psychotropic medications & their combinations. ACCF & AHA recommended an ECG to be done before or 8-12hrs after start of a QT prolonging drugs or its overdose.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

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