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Drug Safety Assessment of escitalopram Usage in its Different Indications with itsRisk-Benefit Profile Management: A Global Review

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ABSTRACT

The aim of this paper is to analyse the patient safety profile of using escitalopram in its different approved indications in addition to identifying, assessing the potential risk (if any), from a review of epidemiological data. The primary focus of the safety monitoring practice is collection, compilation, evaluation and informing of the risk benefit profile of the drug.

Characterizationof escitalopram indications were analysed from different cases reported in various literature sources. Each indication's epidemiology, pathophysiology and risk factors were discussed. Effects of each indication in different population have been identified. Occurrence of incidence with existing medical history was analysed. Internal body parts or chemical factors which may cause those indications have been discussed. General cause of causing these indications has been identified. In addition, the safety concern with identified risk of escitalopram was analysed from The Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) and the important safety concerns were characterized.

Based on the review of available information, the benefit risk profile of escitalopram is positive in its all approved indications. Routine risk minimization measures which include collecting, processing and assessing the individual cases pertaining to escitalopram adverse events are considered sufficient to monitor the benefit-risk profile of escitalopram. So, the selective serotonin reuptake inhibitor, escitalopram can be considered to be one of the most effective and well tolerated medicines for depressed patients.

Key words: Escitalopram; Depression; Risk factor; Anxiety; Panic disorder

1. INTRODUCTION:

Emotions are a critical part of human experience like laugh and cry. But sometimes our emotions are out of control. Sometimes the sadness we feel is not only emotion but depression as well. It turns out that depression is more than just feeling kind of sad. It's actually a neurological condition that can really affect our everyday life. Over the years many classes of antidepressants have become available in India. Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed class of antidepressants. In this study we have consideredescitalopram. The primary focus of this report is measuring the current safety profile of escitalopram with its different indications and analysingits newly identified risk (if any).Therapy with escitalopram is an orally administered Selective Serotonin Reuptake Inhibitor (SSRI). It belongs to the pharmacotherapeutic group of antidepressants and it is indicated for

•Major depressive episodes.

- Panic disorder with or without agoraphobia.
- Social anxiety disorder (social phobia).
- Generalized anxiety disorder.
- Obsessive-compulsive disorder.

This drug exerts a highly selective, potent, and dose-dependent inhibitory effect on the human serotonin transport. By inhibiting the reuptake of serotonin into presynaptic nerve endings, this drug enhances the activity of serotonin in the central nervous system [1].

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Escitalopram is administered as a single daily dose and may be taken with or without food. The dosage of escitalopram for adults with different indication differs. The common dose is 10 mg once a day for major depressive episodes. As per the patient's individual outcome, the daily dose can be modified to a maximum of 20 mg. Usually, in 2 and 4 weeks of treatment the effect of antidepressant can be achieved even though a beginning of the therapeutic outcome is observed prior only. After giving the treatment of the acute depressive episode, it needs a treatment of no less than 6 months for the consolidation of the response. In case of panic disorder, it is advisable to initiate the treatment with a single dose of 5 mg daily for the first week before increasing the dose to 10 mg daily. As per the patient's individual outcome, the daily dose can be increased to a maximum of 20 mg. For social phobia or social anxiety disorder, the dose is 10-20 mg in every 24 hours. For generalized anxiety disorder, the recommended starting dose is 10 mg once a day. If dose increment is required, it should be made minimum after one week. For Obsessive Compulsive Disorder (OCD), the usual dose is 10 mg once a day but the dose can be increased to 20 mg per day accordingly. Because OCD is a continuous long term disease, patients should be treated for an extended period to ensure that they are free of symptoms. This period can be several months or may even longer. When therapy with SSRIs is stopped, a gradual dose reduction should be considered. For children, escitalopram is not advisable since safety and efficacy have not been confirmed with this population [2].

2. MATERIALS AND METHODS

2.1. Characterization of indications

2.1.1. Depression

As per the American Psychiatric Association, depression (major depressive disorder) is a general and serious medicinal disease that unhelpfully affects how people experience, the way they feel and how they act[3]. Depression is categorized as a disorder of frame of mind which may feature unhappiness, difficult to have thoughts and concentration and a significant increase or drop off in hunger and time spent for resting. People who experience depression may have the approach of dejection, sometimes suicidal thoughts and hopelessness [4]. The duration of depression is not fixed and it can be either extended or small.

Epidemiology: In recent decades, there were growing occurrences of depression and depressive symptoms globally. Population studies have constantly shown major depression to be about twice as common in women (from 20% to 25%) as in men (7% to 12%) [5]. Occurrence of depression is more commonly occurred in patients rather than in the general people. First depressive episode are most commonly seen between the age group of 30 and 40, and there is a second, there is a chance of smaller peak of incidence between the age group for 50 and 60[6].

Chronic medical disorders can be considered as significant comorbidity due to depression. The prevalence chronic medical conditions due to depression is different in different conditions including asthma (27%), chronic obstructive pulmonary disease (24.6%), atopic dermatitis (5%), systemic lupus erythematosus (22%), gouty arthritis (20%), chronic obstructive pulmonary syndrome (24.6%), stroke (30%) and rheumatoid arthritis (15%). (**Figure 1)**

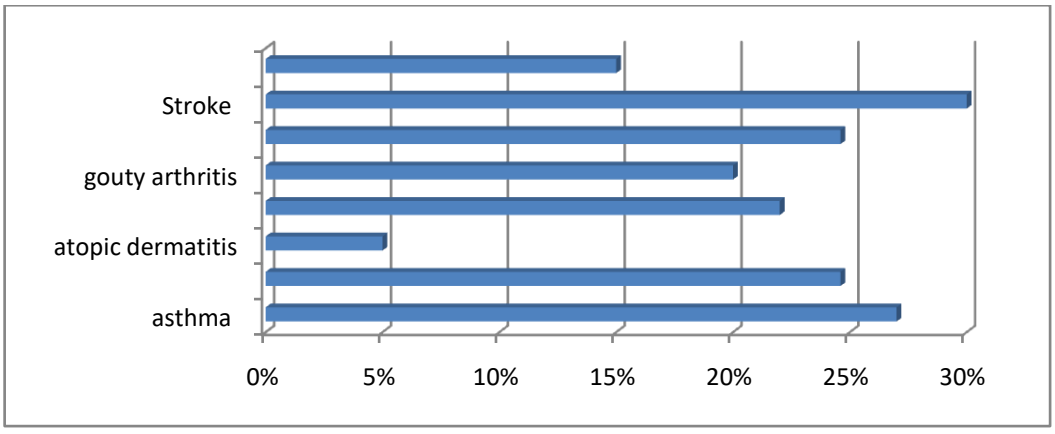

Fig Title:The prevalence to depression is different in different conditions

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There were elevated ($p<0.0001$) occurrence of depression and depressive symptoms in developing countries (24.0%) as compared to developed countries (33.0%). (**Figure 2)**

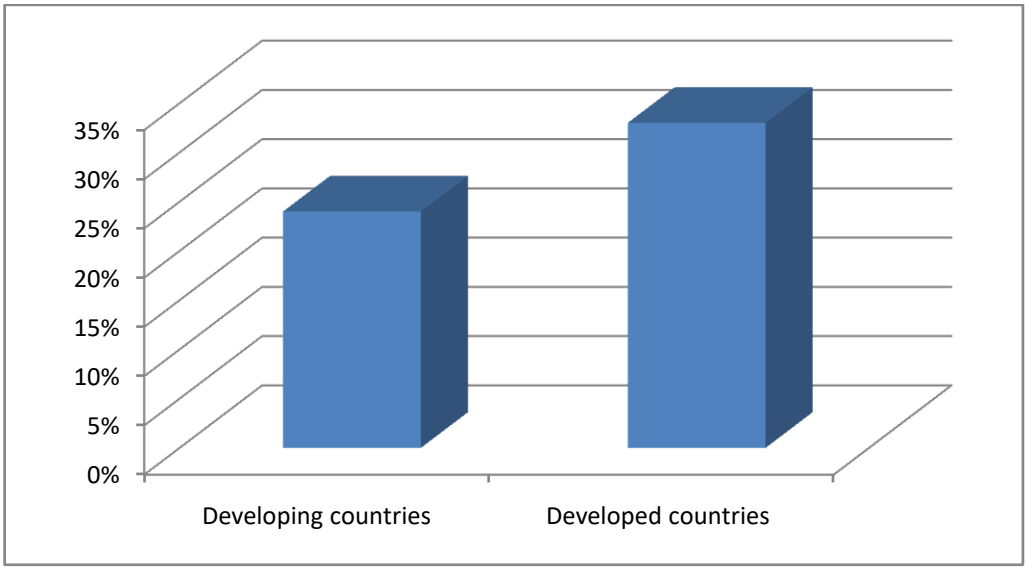

Fig Title:Comparison ofdepression in developing countries with developed countries

Pathophysiology: Numerous factors in arrangement and connection have been concerned in the pathogenesis of depression. These factors comprise neurogenesis, biogenic amine deficiency, immunologic, genetic, endocrine factors and environmental. Ecological stressors and transmissible genetic factors are acting throughout immunologic and endocrine responses and start structural and purposeful changes in many brain parts, ensuing in dysfunctional neurogenesis and neurotransmission which then evident as a group of symptoms which show as depression[7]. Pressure and depression origin neuronal atrophy and defeat in brain parts that manage mood and feeling, consequential in mood disturbance. In count to the well-established function of elevated hypothalamic-pituitary-adrenal (HPA) axis activity, a trademark of anxiety responses, disruptions of neurotrophic/escalation factors have been the focal point of work in current years and could be concerned in the atrophy and beating of neurons in response to pressure and depression[8].

Risk factors:There are several possible factors of depression [9].

Genetic:Depression may be an inherited condition. One has an elevated possibility of experiencing a depressive anarchy at some point in his or her life if that person has a relative with depression. The specific genes implicated for this cause are not identified yet. It's assumed that many genes may take part as a factor in developing depression.

Biochemical: Neurotransmitters in the brain particularly serotonin, dopamine, or norepinephrine influence feelings of cheerfulness and enjoyment and may be abnormal in group with depression. How and why these neurotransmitters become abnormal and what action they do in depressive situation isn't fully stated.

Hormonal: Changes in hormone creation or performing could direct to the beginning of depressive situation. Any differences in hormone situations including childbirth, menopause, thyroid problems or other disorders could cause depression. With postpartum depression, depression can be developed after childbirth in mothers. It's usual to be expressive because of the altering hormones, but postpartum depression is considered to be medically significant condition.

Seasonal: As daytime hours get shorter in the wintry weather, some group grow feelings of laziness, fatigue, and a loss of concentration in everyday actions. This state is called as seasonal affective disorder (SAD). Now it's distinguished as major depressive disorder with recurrent model.

Situational: Trauma, a big alters, or effort in life can cause a case of depression. Losing a dear one, being fired, having monetary difficulty, or having a serious alteration can have a major effect on people.

2.1.2. Panic disorder (PD)

It is a severe, chronic problem characterized by one or more unanticipated panic attacks subsequently worry about added attacks and/or the impacts of the attacks. If attacks are satisfactorily

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severe or recurrent, they can uphold marked, sometimes devastating behavioural alterations. Panic disorder is often associated with increased levels of anxiety, fear of losing control or sanity, or behavioural modification related to the attacks. Feelings of anxiety and fear at definite times are a usual response to the tension or risky situations. But for somebody with panic disorder, experiencing of nervousness, strain and fear occur frequently and at any moment, often for no clear cause.

Epidemiology: Lifetime occurrence of panic attack (PA) was 13.2%. Among people that ever had a panic episode, the greater part had repeated PAs, while only 12.8% satisfied Diagnostic and Statistical Manual version 5 (DSM-5) criteria for panic disorder. Recurring PAs were allied with a consequent onset of a range of mental problems and their course whereas one-time PAs were not. Cross-national lifetime occurrence determines 1.7% for PD with a median age of onset of 32. Around 80.4% people with all-time panic disorder had an existence comorbid mental problem.(**Figure 3)**

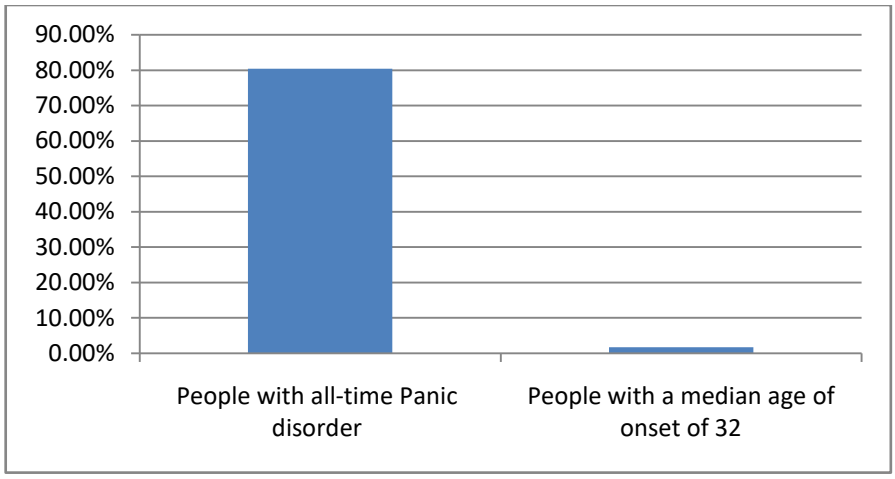

Fig Title: Frequency of PD at different stage of Age

The existence of repeated PAs in specific group is associated with following onset and course of mental disorders beyond agoraphobia and PD, and might provide as a generic threat indicator for psychopathology[10].

Pathophysiology: Amygdala, which acts an essential role in neural system of panic and anxiety, is also alleged to have a significant function in the pathogenesis of PD, even though the neurobiological mechanisms causing panic disorder are not yet apparently stated. As per the neuroendocrinological studies, even though the dysfunction of the hypothalamic-pituitary-adrenal axis takes place only afterward in the course of the disorder after the growth of increased levels of anxiety and linked distress. The brain areas that areconcerned are included amygdala, hypothalamus, thalamus and brain stem parts together with par brachial nucleus, periaqueductal grey and locus coeruleus. The amygdala particularly has been recommended to have an important role in panic disorder [11].

Risk factors:Risk factors of panic disorder included age, female gender and few economic resources. Panic disorder is also believed to beassociated with smoking and alcohol consumption. Few studies also suggested that PD is associated hypermobility of joint and with the number of diseases suffered as well. Panic disorder was also associated with parental psychological disorders, with other anxiety disturbances and psychological health problems in exaggerated group [12].

A careful past story and physical assessment are essential for all patients to find out therapeutic causes of symptoms. Hyperthyroidism and hypothyroidism, temporal-lobe epilepsy, pheochromocytoma, asthma, excessive intake of caffeine, cardiac arrhythmias or other stimulants including withdrawal from alcohol, and dealing with high doses of corticosteroids can imitate or can be the basis of panic attacks. Particular consideration should be given in assessing the existence of depressive symptoms in appropriately treated patients and to stop the suicide threat, keeping in mind that dejected PD patients are less likely responders to treatment than normal subjects.

Factors that may increase the risk of developing panic attacks or panic disorder include:

- Family record of panic episodes
- Most important life stress, such as the death or serious illness of a dear one
- A shocking episode, such as sexual attack or a serious calamity

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- Significant changes in life, such as a separation or the adding a baby in family
- Smoking or extreme caffeine drinking
- History of youth physical or sexual mistreatment

2.1.3. Anxiety

Anxiety has been identified by intense, extreme and constant worry and panic about daily situations. Frequently, anxiety disorders involve repeated episodes of sudden feelings of intense anxiety and fear or terror that reach a peak within minutes (panic attacks). This way of thinking of anxiety and panic interfere with regular tricks, are not easy to manage, are out of part to the real hazard and can persist for an extended duration. Symptoms may trigger in early days or the teenagers and persist into later life. Examples of anxiety disorders consist of panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalized anxiety disorder, separation anxiety disorder and specific phobias.

Epidemiology: Epidemiological studies conclude that anxiety disorders are extremely common and a significant reason of well-designed impairment; they represent the most recurrent mental disorders in the society. Phobias are very regular among which simple phobia and agoraphobiawith the maximum rates. Panic disorder (PD) and obsessive-compulsive disorder (OCD) are uncommon (2% lifetime prevalence), and there are dissonant outcomes for social phobia (SP) (2%-16%) and generalized anxiety disorder (GAD) (3%-30%). These studies use definite diagnostic and evaluation criteria to emphasize the significance of precise description of disorders. The limitations between anxiety disorders are unclear and cases may vary extensively according to the explanation applied. Simple phobia, agoraphobia, and generalized anxiety disorderare more universal while there is no sexual category difference for social phobia, panic disorder, and obsessive-compulsive disorder. Anxiety disorders are more common in separated, detached and widowed persons; their occurrence is highest in the subjects of age between 25 to 44 years and lowest in group aged >65 years. The age of beginning of the different types of anxiety disorders differs widely; phobic disorders start in childhood, whereas panic disorder starts in young adulthood. Risk factors such as life events, childhood experiences and familial factors were identified from Clinical rather than epidemiological studies have examined. Anxiety disorders are often comorbid with other anxiety disorders, depressive disorders and substance abuse. Anxiety disorders most commonly precede depressive disorders or substance abuse. Comorbid conditionmay influence risk factors like functional destruction and class of life. It remains unclear whether definite anxiety disorders (e.g., PD) are risk parameters for suicide. The comorbidity of anxiety disorders has significant impacts for evaluation and treatment; hence the risk factors should be examined [13].

Pathophysiology: The most important mediators of the symptoms of anxiety disorders are dopamine, norepinephrine, and gamma - amino butyric acid (GABA) and serotonin in the central nervous system (CNS). Other neurotransmitters and peptides, for example corticotrophin-releasing factor, are also supposed to be concerned. Peripherally, the autonomic nervous system, particularly the sympathetic nervous system, impacts many of the symptoms. Positron emission tomography (PET) scanning has established bigger flow in the right par hippocampal part and decreased serotonin type 1A receptor binding in the anterior and posterior cingulate and raphe of patients with panic disorder. MRI has confirmed smaller temporal lobe volume in spite of normal hippocampal volume in these patients. The CSF in studies in humans reflects increased levels of orexin, also known as hypocretin which is considered to play a significant role in the pathogenesis of panic in rat models[14].

Risk factors: Trauma; children who undergo abuse or trauma or witnessed traumatic events are at advanced risk of raising an anxiety disorder. Aged who witnessed with a shocking event also can grow anxiety disorders [15].

Stress due to an illness: Having a physical condition or severe sickness can cause important worry about issues such as about their treatment and their prospect.

Stresses build up: An immense event or anescalation of smaller demanding life situations may generate extreme anxiety for example, bereavement in the family, work stress or on-going concern about financial issues.

Personality: Public with definite individuality types are more vulnerable to anxiety disorders than others are.

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Other mental health disorders:Anxiety disorder is also associated with people with other mental health disorders, such as depression.

Having blood relatives with an anxiety disorder can be another cause of having anxiety.

Drugs or alcohol: Drug or alcohol use or misuse or withdrawal can cause or worsen anxiety.

2.1.4. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a general, often unbearable disorder characterized by the occurrence of obsessions and compulsions. Obsessions are common, recurring feelings or images which are experienced as disturbing and not needed, which often cause distinct anxiety and pain. To try to manage the feelings, one feels an irresistible urge to reiterate certain rituals or behaviours. These are known as compulsions.

Epidemiology: The universal occurrence of obsessive-compulsive disorder (OCD) is about 2% of the general people. The males are more frequently affected in childhood and the overturn is true in adulthood. The mean onset age has been noticed as 19.5 years and males are likely to have in prior age of onset than females. Onset of this disorder is uncommon but can happen after age of 35years. The start of symptoms is usually slow and steady. If OCD goes untouched then the course becomes typically chronic with waxing and declining symptoms and reduction rates are low [16].

Pathophysiology: Multiple factors may cause OCD. The genetic variables are concerned: Monozygotic twins are more prone to show OCD symptoms than dizygotic twins. Studies of first-degree relatives have shown that family members are at higher threat. There is an autosomal dominant mode of spread. There is a connection between the development of obsessive-compulsive symptoms and pregnancy. Of late, association of the glutamatergic system in OCD was also considered [17],association of certain polymorphisms in the N-methyl-D-aspartate (NMDA) receptor gene with susceptibility to obsessive-compulsive disorder [18].

There are also some facts signifying the concern of nitric oxide (NO) in OCD. Atmaca et al. (2005) found that there are increased NO levels in plasma of OCD patients as compared to healthy volunteers and that these levels are positively associated with the severity of OC symptoms. The chance that high NO levels are linked to OC symptoms is supported by the truth that SSRI's, anti-dopaminergic drugs and the NMDA receptor antagonist medication known as memantine, all used to treat OCD patients, slow down the production of NO[19].Reports show that in women patients, life events related to the female hormonal cycle may activate or worsen OCD [20]. It's also been suggested that ovarian hormones are having a modulatory role in OCD [21].

Functional neuroimaging studies have elaborated that a hyperactive brain circuit exists in OCD; areas involved include the anterior cingulate, orbitofrontal cortex, striatum and thalamus. In alleviating obsessions and compulsions in patients, deregulation of the serotonergic (5-HT) system has been recommended primarily on the basis of the usefulness of SRI's and selective serotonin reuptake inhibitors (SSRI's)[22]. After administration of selective serotonin reuptake inhibitors (SSRIs) or cognitive-behavioural therapy, a decrease in metabolic activity in the hyperactive brain circuit has been shown to occur. Additionally, some patients have an exacerbation of OCD symptoms following beta-haemolytic streptococcal infection.

Risk factors: Age; OCD appears to develop in late teenage years or early adulthood. Though, it can begin as early as nursery age and as late as age 40 years as well [23].

Genetic Factors: Research shows that genes may act a role in the development of OCD in few cases. The state tends to pass in families. A person who has OCD has a 25% chance of having a blood relative who has it. One study found that kids have inborn OCD symptoms in 45% to 60% of cases, while adults have inborn symptoms in 27% to 47% of cases.

Presence of Other Mental or Neurologic Conditions: OCD often appears in peoplewho have other anxiety disorders, substance abuse, depression, and attention-deficit hyperactivity disorder (ADHD), Tourette syndrome, eating disorders and certain personality disorders.

Stress: OCD symptoms frequently occur during stress from major life changes, such as the loss of a dear one, separation, relationship difficulties and issues in school or abuse.

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Pregnancy and Postpartum Period: OCD symptoms may deteriorate during and instantaneously after pregnancy. In this case, irregular hormones can trigger symptoms. Postpartum OCD is identified by disturbing thoughts and compulsions regarding the baby's well-being.

Important safety concern associated with escitalopram:The safety of escitalopram was assessed from Co-ordination group for Mutual recognition and Decentralised procedures-human (CMDh).Up to 5% of the population report having been depressed in the previous year, and as many as 13%report being depressed intheir lifetime. Frequency of depression is twice in women as in men. The risk of death by suicide associated with low mood and feeling of worthlessness is 20 times more frequent in depressed individuals than in the general population. There is 60% increased incidence of type II diabetes and cardiovascular diseases in depressed patients.Approximately 20% of the populations experienced an anxiety disorder at some point during their life. With the exception of obsessive compulsive disorders, women are at greater risk. While the major risk of OCD lies in suicide, major risks related to anxiety disorders are the confusion of somatic symptoms with somatic diseases. Depression and anxiety disorders are very often co morbid.Daily life and quality of life can be much impacted by these conditions [24].

The below safety concerns were identified for escitalopram during this review [25]:

Important Identified Risks	Electrocardiogram QT prolongation
Important Potential Risks	None
Missing Information	Use in pregnancy and lactation

3. RESULTS

Characterization of Important Identified Risk

Electrocardiogram QT prolongation: Exact frequency of QT interval prolongation is not known. No information related to consequence of QT interval prolongation with escitalopram is available.It is recommended to establish and maintain the permeability of the airways, to ensure adequate oxygenation and respiratory function. After oral ingestion of the medication,gastric lavage should be performed as soon as possible. It is recommended to control the vital and cardiac signs in addition to establishing the measures of symptomatic support. In a clinical trial in Japan, the QT interval was examined with Fridericia's correction formula (QTcF = QT/cubic root of relative risk). There was no difference in the QTcF values between escitalopram (10mg/day)received patients and placeboreceived patients. However, QTcF was significantly prolonged with escitalopram (20 mg/day) treated patients as compared to with placebotreatedpatients.There were no clinically problematic adverse events related to QT prolongation. The trial report stated that caution was required in administering escitalopram to elderly patients, patients with liver dysfunction, patients with defective CYP2C19 activity, or patients who received other drugs that can cause a risk of QT prolongation[26].

Precautionary statement with the use of escitalopram: Forescitalopram only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Therapy with escitalopram should not be used during pregnancy unlessclearly necessary and only after careful consideration of the risk/benefit. Neonates should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester.

Abrupt discontinuation should be avoided during pregnancy [27]. It is expected that escitalopram will be excreted into human milk. Consequently, breast-feeding is not recommended during escitalopramtreatment.

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4. DISCUSSION

This review provides an overview of escitalopram including its mechanism, indication and patient acceptability in the management of its different approved indications. In addition, escitalopram exerted a stable ant depressive action. The adverse events related to escitalopram therapy were generally mild and temporary; hence it has a high tolerability. As the major depressive disorder (MDD) can recurs readily, it is more important to select the antidepressant drugs that allow high therapy continuity for treatments.Based upon review of available information, the benefit risk profile of escitalopram is positive in its all indications.Routine risk minimization measures are considered sufficient to monitor the benefit-risk profile of escitalopram.

5. CONCLUSION

Collecting, processing and assessing the individual cases pertaining to escitalopram adverse events and to report the same to different Health Authorities are very important to assess the routine safety profile of using escitalopram. However all manufacturing pharmaceutical companies are liable to report a cumulative data with a specific frequency to the different local Health Authority to assess the benefit risk profile of this drug. These are the part of routine safety assessment activity. As of now, no additional risk minimizations measures (Educational tools/ Controlled access programme/ Pregnancy prevention programme etc.) are requiredsince the current available data do not support the need for additional risk measurement activities. However, the risks will be monitored and, if necessary, measures will be established according to the type of risk. So, the Selective Serotonin Reuptake Inhibitor (SSRI), escitalopram can be considered to be one of the most effective and well tolerated agents for the treatment of moderate and severe major depressive disorder, as well as for the treatment of anxiety disorders.

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7. CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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