Usage of Paroxetine, Fluoxetine, Olanzapine and Divalproex in Bipolar and Panic disorder

Content

Background and Objective of the Survey

Bipolar disorder, previously known as manic-depressive disorder, is a chronic disorder characterized by abnormal mood changes and fluctuation in energy levels. The disease is characterized by an individual spiraling into a state of melancholy, which can last up to a few months and is known as a depressive episode. Bipolar disorder is the result of an imbalance in neurotransmitters in the brain (serotonin, dopamine and noradrenalin).

Panic disorder is a common mental disorder that affects up to 5% of the population at some point in life. It is often disabling, especially when complicated by agoraphobia, and is associated with substantial functional morbidity and reduced quality of life. The disorder is also costly for individuals and society, as shown by increased use of health care, absenteeism, and reduced workplace productivity.

Paroxetine is unique among the SSRIs because in addition to its effect on the CNS serotonergic neurotransmission, it also has mild noradrenergic properties. Paroxetine was the first SSRI approved for the treatment of panic disorder and its efficacy is well-established in the short-term treatment of patients with panic disorder.

Fluoxetine is a bicyclic monoamine whose primary pharmacological action is selective inhibition of serotonin (5-hydroxytryptamine; 5-HT) reuptake. This action appears to be necessary for the treatment of obsessive-compulsive disorder (OCD).

Olanzapine is a second-generation antipsychotic agent that exhibits a wide array of receptor affinities. Olanzapine-fluoxetine combination (OFC) therapy and quetiapine are the only FDA approved medications for the treatment of acute bipolar depression.

Divalproex is the most commonly prescribed anticonvulsant medication for patients with bipolar disorder, with prescription rates similar to lithium. Divalproex has demonstrated efficacy in preventing depressive episodes during maintenance treatment.

The objective of the survey is:

To study the usage of paroxetine, fluoxetine, olanzapine and divalproex in bipolar and panic disorder.

Methodology of the Survey

A survey was conducted to study the usage of paroxetine, fluoxetine, olanzapine and divalproex in bipolar and panic disorder. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Overview of panic and bipolar disorder
- Risk factors – panic and bipolar disorder
- Pathophysiology – panic and bipolar disorder
- Treatment – panic and bipolar disorder
- Paroxetine
- Fluoxetine
- Olanzapine
- Divalproex

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Overview of panic and bipolar disorder

Bipolar disorder

Major depressive episodes are a prominent symptom in both bipolar disorders and major depressive disorder (MDD), which is the reason that up to 69% of patients with bipolar disorders are misdiagnosed. Bipolar disorder, previously known as manic-depressive disorder, is a chronic disorder characterized by abnormal mood changes and fluctuation in energy levels. The disease is characterized by an individual spiraling into a state of melancholy, which can last up to a few months and is known as a depressive episode. The typical presentation of these episodes of depression includes low energy levels, hypersomnia, cognitive impairments, decreased sexual desire, carbohydrate craving, and weight gain. Suicide attempts are extremely common during such an episode and individuals have confessed to being in a very dark space with no other way to escape. Conversely, bipolar disorder also has a stage of exhilaration and excitement, which can be classified as a manic episode. The typical presentation of these episodes of mania includes high energy hallucinations and delusions, sleep deprivation, fast speech and a constant need to be active.[1]

Bipolar disorder can be divided into a number of sub-types based on the identification of specific mood episodes, namely:[1]

- Bipolar I disorder
- Bipolar II disorder
- Cyclothymic disorder
- Substance/medication induced bipolar and related disorder
- Bipolar and related disorder due to another medical condition
- Other specified bipolar and related disorder
- Unspecified bipolar and related disorder

Individuals with bipolar disorders type I experience periods of severe mania and short depressive episodes, which usually follow the manic phase directly. It can also present as mixed episodes. Individuals with bipolar disorders type II experience episodes of hypomania and severe depression, which is regularly misdiagnosed as major depression disorder. 1 Individuals diagnosed with unipolar disorder present with symptoms of a chronic sub-syndromal depressive state2 which is also often misdiagnosed as major depressive disorder.[1]

Manic phase	Depressive phase
• High energy • Hallucinations • Delusions • Sleep deprivation • Fast speech • High levels of activity	• Loss of interest in activities • Fatigue • Agitation • Thoughts of death • Weight loss/gain • Poor concentration • Feelings of worthlessness • Sleeping too little

Figure 1. Signs and symptoms of the manic and depressive phases of bipolar disorder[1]

Cyclothymic disorder presents with chronic fluctuations between sub-syndromal depressive and hypomanic episodes. Longitudinal assessment and detection of hypomanic periods are crucial to differentiate bipolar disorders from other conditions. Bipolar disorder type I is experienced by more than 0.8% of the world's population, and around 1.1% of the population for bipolar disorders type II. This condition does not discriminate in terms of gender, race, nationality, social economy class or level of education. There is an equal distribution in males and females, but males tend to experience the manic phase more commonly and females the depressive phase. Genetic components play a role in the diagnosis of bipolar disorders, where first-degree relatives with bipolar disorders will increase one's chances of suffering the disease. The usual age of onset is late adolescence and early adulthood, although some cases in children have been reported. In many communities, bipolar disorders is not recognized as an illness, hence many people suffer in silence.[1]

Panic disorder

Panic disorder is a common mental disorder that affects up to 5% of the population at some point in life. It is often disabling, especially when complicated by agoraphobia, and is associated with substantial functional morbidity and reduced quality of life. The disorder is also costly for individuals and society, as shown by increased use of health care, absenteeism, and reduced workplace productivity. Some physical illnesses (e.g., asthma) commonly occur with panic disorder, and certain lifestyle factors (e.g., smoking) increase the risk for the

disorder, but causal pathways are still unclear. Genetic and early experiential susceptibility factors also exist, but their exact nature and pathophysiological mechanisms remain unknown. Despite an imprecise, although increased, understanding of cause, strong evidence supports the use of several effective treatments (e.g., pharmacological, cognitive-behavioral). The adaptation and dissemination of these treatments to the frontlines of medical-care delivery should be urgent goals for the public health community.[2]

Although panic disorder emerged as a diagnostic entity only 25 years ago with the publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III, accounts of a clinically similar syndrome have appeared much earlier (e.g., Da Costa's soldiers' heart, Wheeler's neurocirculatory asthenia, and Lewis's effort syndrome). Along with paroxysmal autonomic nervous system arousal and catastrophic cognitions, these descriptions highlighted symptoms of profound fatigue, which are not part of current diagnostic criteria. The military contexts in which these syndromes developed implicated a prominent role for stress and trauma, suggesting a possible area of causal overlap with post-traumatic stress disorder, another anxiety illness that often includes panic attacks. Of all the anxiety-related syndromes, panic disorder has been the most intensively studied during the past 25 years, has advanced our understanding of the psychology and neurobiology of anxiety, and has helped dispel the notion that anxiety is a trivial problem (i.e., affecting worried yet well individuals) not needing definitive treatment.[2]

Risk factors

For developing bipolar disorder

Risk factors that contribute to bipolar disorders include the use of cannabis, one to four times per week, influenza during the third trimester of pregnancy, as well as smoking during pregnancy, which may affect the fetus. In addition, such risk factors may also include the use of cocaine, the use of opioids, tranquilizers, stimulants and sedatives during pregnancy, and regular substance use during a period of a year. Parental loss before the age of five, war trauma and stress, as well as traumatic head injury may influence the condition. Factors that may worsen the condition in a diagnosed individual may include the use of alcohol, opioids, tranquilizers, stimulants and sedatives. Anxiety disorders, socio-economic problems, child abuse and sexual maltreatment may also worsen the condition.[1]

For developing panic disorder

Factors that increase the salience of bodily sensations are central to the onset of panic disorder. One such factor is anxiety sensitivity, the belief that anxiety could cause deleterious physical, social, and psychological consequences that extend beyond any immediate physical discomfort during a panic attack. Anxiety Sensitivity Index values predict the onset of panic attacks in adolescents, university students, and community sample groups, even after previous depression is controlled for, and also predict spontaneous panic attacks and worry about panic during 5 weeks of basic military training, even after history of panic attacks and trait anxiety are controlled for. However, anxiety sensitivity accounts for less of the variance in panic disorder onset than neuroticism, or proneness to have negative emotions in general. Anxiety sensitivity could be acquired insidiously from a lifetime of direct aversive experiences (i.e., personal history of severe illness or injury), vicarious observations (i.e., severe illnesses or death among family members), informational transmissions (i.e., parental warnings), or parental reinforcement of attention to somatic symptoms and parental modelling of distressed reactions to bodily sensations. Finally, panic attacks themselves increase anxiety sensitivity. The peak in prevalence between ages 15 and 19 years possibly occurs because of the added salience of bodily cues at that stage of psychosocial development, due to sexual development and hormonal changes.[2]

Pathophysiology

Bipolar disorder

Theoretically, bipolar disorders is the result of an imbalance in neurotransmitters in the brain (serotonin, dopamine and noradrenalin). A dysregulation between the excitatory (noradrenaline (NA), dopamine (DA), glutamate and aspartate) and inhibitory neurotransmitters (serotonin (5-HT) and GABA) has an effect on the normal neuronal transmissions in the brain. Serotonin is seen as an inhibitory neurotransmitter due to the effect it has on decreasing acetylcholine release, where an excess thereof results in depression. In the monoamine hypothesis, an excess of catecholamines, namely NA and DA, causes mania, while the exact opposite is found when there is a deficit of neurotransmitters, namely NA, DA and 5-HT, which will cause depression.[1]

An increase in the concentration of NA in the cortical and thalamic areas of the brain is evident in studies of bipolar disorders individuals. Noradrenalin and its metabolite 3-methoxy-4-

hydroxyphenyl glycol (MHPG) tend to be lower during the depressive phase and higher during the manic phase of bipolar disorders. High levels of MHPG have been identified in urine and cerebrospinal fluid during the manic phase of bipolar disorders.[1]

The cholinergic hypothesis states that a deficiency of acetylcholine causes an imbalance in cholinergic-adrenergic activity and can increase the risk of manic episodes, whereas an increased level of acetylcholine activity will result in depressive episodes. The hypothalamic-pituitary-thyroid axis dysregulation hypothesis states that hyperthyroidism can cause manic-like symptoms and hypothyroidism may cause depression. Hormonal changes during the female life cycle can cause dysregulation of neurotransmitters (e.g., premenstrual, postpartum, and perimenopause).[1]

Calcium concentrations, both intra- and extra-cellular, may affect the synthesis and release of NA, DA, and 5-HT, as well as the excitability of neuronal firing. Through this mechanism, abnormal calcium and sodium activity can cause neurotransmitter dysregulation, such as hypocalcemia that has been associated with mood irritability, anxiety, mania and psychosis. Hypercalcemia has been associated with depression, stupor, and coma.[1]

Panic disorder

Genetic susceptibility

Panic disorder, similar to other psychiatric disorders, is thought to be complex with many genes conferring vulnerability through unknown pathways. Panic might exist in many distinct genetic forms, each with a different set of genes, or it could exist in one form with an underlying set of genes that reflect a broad vulnerability to panic and anxiety. Evidence has supported a specific type of panic disorder associated with bladder problems (possibly urinary interstitial cystitis) that is linked to locus q32–33 on chromosome 13. An association study also related this same chromosomal region to panic disorder, irrespective of associated features. A subtype of bipolar illness associated with panic attacks has been linked to a locus on chromosome 18 and might show clinical differences from other forms of bipolar illness (i.e., rapid mood switching and increased familial risk for affective illness), although these findings are neither consistent nor robust. The exact genes, gene products, or functions related to the genetic regions implicated in both these phenotypes of panic disorder remain unknown. Finally, a genome-wide scan of

an Icelandic cohort revealed linkage on chromosome 9q31, which has also been linked to cigarette smoking. This common region is notable because of the previously reported association between teenage smoking and adult risk of panic disorder and could constitute another possible phenotype of the disorder.[2]

Other studies have focused on genes judged to have functional importance in anxiety pathophysiology. A genome-wide scan implicated regions on chromosome 1, consistent with QTL (quantitative trait loci) studies linking anxiety to this locus in both healthy human beings and mice and to chromosome 11p at a marker for the cholecystokinin-B (CCK-B) receptor gene, consistent with the known ability of CCK to precipitate panic attacks in some individuals with panic disorder. However, not all studies have shown an association between the CCK-B gene and the disorder. Finally, both association and linkage studies have implicated the adenosine 2A receptor gene in panic disorder, consistent with the anxiogenic effects of caffeine (a known antagonist of this receptor) and with the finding that allelic variations in the gene have been associated with caffeine-induced anxiety.[2]

Association studies of genes in neurotransmitter systems thought to be associated with fear and anxiety (e.g., norepinephrine and serotonin) have produced inconsistent, often non-replicated results. The most consistent data implicate the gene for 22q11 catechol-o-methyltransferase (COMT) that codes for the enzyme responsible for norepinephrine metabolism. Linkage and association studies have implicated this region of chromosome 22. By contrast, two association studies have failed to link the norepinephrine transporter to panic disorder and most studies of serotonin-related genes have been negative, including the serotonin-transporter-promoter region previously linked to anxiety states in general, the serotonin 1A receptor, and the serotonin 2C receptor. Only one study has shown an association between the serotonin 2A receptor gene and panic disorder.[2]

Several of these negative studies have compared panic disorder with and without agoraphobia and have shown some positive findings for the agoraphobia subgroup, although with variable and inconsistent data. These investigations have been restricted because of not having enough knowledge about the pathophysiology of panic disorder, nor able to identify the most heritable phenotypes of the illness. However, the failure to replicate genetic associations is not a problem

for panic disorder only, and shows inherent difficulties in the extant association approaches to complex genetic diseases. Genome-wide association methods will be used to study panic disorder further, complemented by the scrutiny of gene-environment interactions.[2]

Current standard treatment modalities and their efficacy

Panic disorder

Significant progress has been achieved concerning the presumed biological basis and the pharmacotherapy of panic disorders. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly recommended first-line and second-line pharmacotherapies, followed by a number of switching strategies, while cognitive-behavior therapy (CBT) is the first-line psychological treatment. However, a significant proportion of panic disorder patients shows little or no response to standard pharmacotherapies, CBT and/or their combination, and suffer from significant and impairing residual symptoms. The remission rates achieved with pharmacotherapy range between 20% and 50%, and approximately 20% of patients will remain substantially impaired despite undergoing a succession of pharmacological and/or psychosocial treatments. Therefore, panic disorder is considered a potentially chronic, recurrent and often difficult-to-treat psychiatric illness.[3]

Despite the official guidelines, which consider pharmacotherapy with antidepressants alone and CBT alone as two treatment modalities with similar efficacy, some research data suggest that psychopharmacological treatment may be somewhat more effective than psychotherapies – including CBT – especially for more severely ill patients with panic disorder without or with agoraphobia (PDA). It remains uncertain whether combined CBT-pharmacotherapy is substantially more effective than either approach given as monotherapy. There is a need for novel interventions that might enable non-responders or partial responders to become full-responders to treatment. Drugs with proven efficacy and acceptability in patients with other psychiatric conditions might conceivably be suitable for ‘repurposing’ in patients with treatment-resistant panic disorder.[3]

Bipolar disorder

Novel treatments for bipolar disorders target disparate effector systems, including molecular targets that participate in neuroplasticity, neurotrophism, apoptosis, inflammation, oxidative and nitrosative stress, mitochondrial function, and metabolic pathways. Examples of such novel treatments are coenzyme Q10, N-acetyl cysteine, statins, non-steroidal anti-inflammatory agents, omega-3 fatty acids, incretin-based therapies, insulin, nitrous oxide, ketamine, prebiotics, probiotics, and antibiotics.[4]

Considerable attention is being given to the possibility of altered gut microbial diversity as relevant to the disease process and comorbidity in bipolar disorders. Replicated evidence indicates that adults with bipolar disorders show decreased gut microbial diversity relative to healthy controls or unaffected first-degree relatives. Notwithstanding, interventional recommendations with gut microbiota modulators (e.g., prebiotics and probiotics) cannot be recommended at present. A promising clinical application is the antibiotic minocycline, which has been reported in open-label trials to attenuate depressive symptoms in people with bipolar disorders and has been evidenced in controlled trials to attenuate depressive symptoms in people with major depressive disorder. It should be noted that rigorous randomized controlled trials have not found efficacy for minocycline in the treatment of people with bipolar depression. However, whether the effects of minocycline in patients with bipolar disorders are mediated via the gut microbiome or via other pathways (e.g., microglial stabilization and anti-inflammation) is unknown.[4]

Racemic ketamine has shown efficacy in single dose and repeat dose administration in adults with bipolar disorders. The advantages of ketamine include rapid symptom attenuation, efficacy in treatment-resistant severe, and persistent depression, and possible antianhedonia and anti-suicide effects. Ketamine does not appear to induce hypomanic, manic, or psychotic symptoms at a rate higher than that of placebo; nevertheless, the absence of safety and efficacy data, and the possibility of misuse, diversion, and gateway activity predicated on ketamine's opioid mechanisms, cannot be ruled out when used in people with bipolar disorders. Preliminary evidence also suggests that intravenous ketamine might reduce suicidality (i.e., suicidal ideation) in adults with mood disorders.[4]

Meta-analytic evidence for N-acetyl cysteine has been mixed. Moreover, evidence for most anti-inflammatory agents as treatments for bipolar disorders is limited by considerable heterogeneity in trial design and methodology. Preliminary evidence suggests that anticytokine therapy (e.g., infliximab) attenuates the severity of depression symptoms in adults with bipolar disorders reporting a history of sexual abuse. Preliminary evidence also suggests that incretin-based therapies might mitigate depression and cognitive symptoms in adults with mood disorders.[4]

An additional potential therapeutic avenue in bipolar disorders is the targeting of central neurosteroids. The efficacy of intravenous brexanolone, a positive allosteric modulator of γ-aminobutyric-acid (GABA) type A receptors, in post-partum depression suggests potential efficacy for this agent in bipolar depression. The availability of an oral formulation of brexanolone and the efficacy of brexanolone in major depressive disorder provides the impetus for further testing of brexanolone in people with bipolar disorders.[4]

Chronobiological disturbances are central to the pathogenesis and phenomenology of bipolar disorders. Lithium targets key molecular systems (i.e., GSK-3 beta) that are implicated in cellular rhythms and are thought to be relevant to lithium's mechanism of action. Adjunctive bright light therapy (i.e., 7000 lx) has shown efficacy in the treatment of adults with bipolar depression without exacerbating hypomanic symptoms and should be considered a treatment alternative when more conventional approaches are insufficient. Hitherto, melatonin-based treatments have not been reported to be efficacious in bipolar disorders; a testable hypothesis is that orexin-based therapies (e.g., suvorexant) might be viable therapeutic agents in individuals with mood disorders. Despite the unmet needs in bipolar disorders with existing treatments and the promise of mechanistically dissimilar novel agents, these foregoing investigational agents cannot be considered efficacious or safe in the treatment of bipolar disorders. Moreover, some agents (e.g., folic acid) might reduce the efficacy of mood stabilizers. Nevertheless, novel targets are being exploited in therapeutic research to improve upon existing treatments for bipolar disorders and to identify novel approaches to modify disease.[4]

Paroxetine

Paroxetine is unique among the SSRIs because in addition to its effect on the CNS serotonergic neurotransmission, it also has mild noradrenergic properties. Paroxetine was the first SSRI approved for the treatment of panic disorder and its efficacy is well-established in the short-term treatment of patients with panic disorder.[5]

Pharmacodynamic and pharmacokinetic profile

Paroxetine is well-absorbed from the gastrointestinal tract, reaching peak concentrations in 2–8 h. The absolute bioavailability ranges from 50 to 100%. Its absorption in not influenced by food. As with other SSRIs, protein binding of paroxetine is very high (95%). It undergoes extensive first pass metabolism in the liver. Metabolism is accomplished in part by cytochrome P4502d6, partial saturation of this enzyme at clinical doses appears to account for the nonlinear kinetics observed with increasing dose and duration of treatment. The elimination half-life is approximately 24-h with a range of 3 to 65 h. Steady-state concentration is achieved within 7–14 days of drug initiation. The routes of elimination are urinary and fecal excretion and the half-life is prolonged in patients with severe renal or hepatic function impairment.[5]

A number of important pharmacokinetic and pharmacodynamic drug interactions are observed with paroxetine. All SSRIs can potentially produce a fatal hypermetabolic syndrome when given together with a MAOI. Paroxetine inhibits the P4502d6 isoenzyme, causing elevated levels of any co-administered drug also metabolized by this enzyme. Drugs metabolized by this enzyme include cimetidene, haloperidol, tricyclic antidepressants and some antiarrhythmic agents, such as flecainide. In addition, paroxetine is highly bound to plasma proteins and can displace other drugs, such as carbamazepine, phenytoin and warfarin from their protein binding sites.[5]

Clinical profile

Oehrberg and colleagues compared the efficacy of short-term paroxetine treatment with placebo and found that paroxetine was significantly superior to placebo in all primary measures of outcome including a 50% reduction in the total number of panic attacks and panic attacks reduced to one or zero over the study period. In another double-blind, placebo-controlled study, Ballenger reported that 86% of panic disorder patients became panic-free following 10 weeks

of 40 mg per day paroxetine treatment. Additional short-term studies with paroxetine have also demonstrated high recovery rates and confirm previous findings that paroxetine at all doses is well-tolerated.[5]

Several studies have also examined the efficacy of intermediate-term (6–12 months) paroxetine treatment. Judge and colleagues assigned patients with panic disorder who had responded to 3 months of paroxetine treatment to continue to receive either an additional 3 months of paroxetine maintenance treatment or placebo. The patients who continued to receive paroxetine had a 5% relapse rate compared with 30% among those who crossed over from paroxetine to placebo. Lecrubier and colleagues examined patients who completed 12 weeks of paroxetine treatment and then entered a 36-week extension phase of either paroxetine, clomipramine or placebo. The number of panic attacks per week amongst the paroxetine and clomipramine group continued to fall during the maintenance phase. By the end of the maintenance phase, 84.6% of the paroxetine group recovered completely (0 panic attacks per week compared with 59.1% among the placebo group. The results of these and other studies led to the current American Psychiatric Association (APA) recommendation that SSRI pharmacotherapy should be continued for at least 1 year.[5]

Therapeutic potential

In 3 short term placebo-controlled trials in patients with panic disorder with or without agoraphobia, oral paroxetine 10 to 60 mg/day is significantly more effective than placebo for most variables measuring reduction in panic attack frequency. The drug also produced significantly greater improvements in various anxiety and depression scales than placebo. An extension phase of one of the placebo-controlled studies showed that the efficacy of paroxetine in reducing panic attack frequency is maintained during up to 6 months' treatment and that the drug reduces the risk of relapse. Oral paroxetine 10 to 60 mg/day was at least as effective as clomipramine 10 to 150 mg/day in a comparative study. During weeks 7 to 9 of treatment, 51 % of paroxetine recipients had no full panic attacks, compared with 37% of clomipramine recipients. The onset of action appeared to be more rapid for paroxetine than for clomipramine. The 2 drugs were equally effective in improving generalized anxiety, phobic avoidance and social, family and work interactions. In patients who elected to continue treatment for a further 36 weeks in an extension phase of the above study, response rates increased further in all

groups, including the placebo group. During weeks 34 to 36 of extended treatment, 85% of paroxetine recipients, 72% of clomipramine recipients and 59% of placebo recipients had no panic attacks. The difference between paroxetine and placebo was statistically significant at this time point; however, there was no significant difference between groups at the primary efficacy endpoint (weeks 22 to 24).[6]

Tolerability

Paroxetine is generally well tolerated by both younger and older individuals and its adverse event profile is consistent with that expected for an SSRI. The tolerability profile of paroxetine in patients with panic disorder appears to resemble that in patients with depression. Headache, nausea, somnolence, dry mouth and insomnia were the most common adverse events among 469 patients with panic disorder who received paroxetine 10 to 60 mg/day in short term clinical trials. The individual incidences for these events ranged from 18 to 25%; however, the incidence of headache in paroxetine-treated patients was the same as that in placebo recipients. Nausea was the most commonly cited reason for adverse event-related discontinuation of paroxetine treatment. Asthenia, sweating, constipation, dizziness, tremor and diarrhea were reported by >5% of paroxetine recipients and occurred more commonly than in placebo recipients. Laboratory parameters and hepatic and renal function are not generally affected to any clinically significant extent by paroxetine treatment, but hyponatremia has been reported rarely.[6]

Abnormal ejaculation was reported by 21 % of men treated with paroxetine for panic disorder. Trials in patients with depression have suggested that paroxetine is associated with higher incidences of nausea and abnormal ejaculation (mainly delayed ejaculation) than comparator tricyclic and tetracyclic antidepressants. However, this was not the case in a comparative study of paroxetine versus clomipramine in patients with panic disorder. Furthermore, patients rarely discontinue paroxetine treatment because of abnormal ejaculation. In the comparative study, paroxetine 10 to 60 mg/day was better tolerated overall than clomipramine 10 to 150 mg/day and was associated with a lower incidence of certain anticholinergic effects (dry mouth, constipation). Paroxetine was also better tolerated overall than tricyclic or tetracyclic antidepressants in clinical trials involving patients with depression. Clinically significant bodyweight gain during long term treatment is less of a problem with paroxetine than with

comparator drugs. Extrapyramidal adverse events and seizures have been reported to occur only very infrequently in paroxetine-treated patients. The drug appears to have a low potential for precipitating mania in patients with unipolar or bipolar depression. Paroxetine is not associated with physical or psychological dependence. However, when paroxetine is discontinued, a small percentage of patients may experience transient symptoms such as dizziness, sweating, nausea, diarrhea, insomnia, headache and fatigue. Paroxetine appears to be safer in overdose than the tricyclic agents: a fatal outcome has been reported only on rare occasions.[6]

Dosage and administration

The recommended starting dosage of paroxetine for the treatment of panic disorder with or without agoraphobia is 10 mg/day taken orally as a single dose. The dosage can be increased in 10 mg/day increments at I-week intervals to a maximum of 60 mg/day. The dosage should not exceed 40 mg/day in elderly or debilitated patients or those with severe renal or hepatic impairment. Paroxetine should not be used during pregnancy or breast feeding unless the potential benefit to the mother justifies the potential risk to the infant. Caution is required when using paroxetine in patients with a history of epilepsy or mania. MAOI therapy must be discontinued at least 2 weeks before the initiation of paroxetine treatment and must not be initiated until at least 2 weeks after paroxetine therapy has been discontinued. When stopping paroxetine treatment, tapering of the dosage over several weeks may reduce the risk of discontinuation symptoms.[6]

Fluoxetine

Fluoxetine is a bicyclic monoamine whose primary pharmacological action is selective inhibition of serotonin (5-hydroxytryptamine; 5-HT) reuptake; this action appears to be necessary for, but does not fully explain, its efficacy in the treatment of OCD. It inhibits the reuptake of other neurotransmitters to a much lesser extent and has little affinity for a number of neurotransmitter binding sites. The mean elimination half-lives of fluoxetine and its active metabolite norfluoxetine are 2 to 7 and 7 to 15 days, respectively, after multiple doses.[7]

Results of several short-term clinical trials indicate that fluoxetine 20 to 80 mg/day is superior to placebo in reducing OCD symptom scores, with significant effects seen in both obsessive

and compulsive subscores. Response rates of 32 to 48% for fluoxetine-treated patients compared with response rates of 8 and 26% for patients treated with placebo have been reported. Significant improvement in symptoms compared with placebo were reported after 4 to 8 weeks of treatment. While adequate comparative trials are not available, meta-analysis of data from large placebo-controlled trials found fluoxetine to be similarly effective to fluvoxamine and sertraline, but less effective than clomipramine. Studies in patients with OCD and concurrent depression or Gilles de la Tourette S syndrome have also found fluoxetine to be effective in reducing OCD symptoms.[7]

Fluoxetine has been used in combination with a variety of agents including buspirone, lithium, clomipramine and fenfluramine in an attempt to augment the response in patients with treatment-refractory OCD, although adequate data to support this approach are lacking. In comparison with tricyclic antidepressants, fluoxetine causes less sedation, fewer anticholinergic or cardiac adverse effects and is less harmful in overdose, although certain CNS activating effects (insomnia, anxiety, anorexia) and gastrointestinal effects (nausea, diarrhoea) are more frequent with fluoxetine. The overall evidence presently suggests that fluoxetine is an effective agent in the treatment of OCD, although its relative efficacy and tolerability compared with other pharmacological treatments remain to be established. While several questions concerning its ultimate role in the treatment of OCD remain unresolved, fluoxetine should currently be considered as a useful treatment option with a tolerability profile that makes it especially attractive for patients less likely to tolerate the anticholinergic and cardiac adverse effects of clomipramine.[7]

Pharmacodynamic properties

Fluoxetine and its active metabolite norfluoxetine are potent and selective inhibitors of serotonin (5-hydroxytryptamine; 5-HT) reuptake. They inhibit the reuptake of noradrenaline (norepinephrine) and dopamine to a much lesser extent. Fluoxetine also has little binding affinity for αl-, α2- and β-adrenergic, histamine H1, histamine H2, muscarinic, serotonergic, opioid, γ-aminobutyric acid (GABA)-benzodiazepine or dopaminergic receptors. Results from animal studies indicate that exposure to fluoxetine for >10 days results in downregulation of somatodendritic and terminal 5-HTI auto receptors and has variable effects on 5-HT2 receptors. Positron emission tomography in patients with OCD has revealed increased metabolic activity

within the basal ganglia and limbic, thalamic and cortical brain regions compared with healthy volunteers. In patients with OCD who responded to treatment (including fluoxetine), normalisation of glucose metabolism in orbitofrontal regions or in the right caudate nucleus has been reported.[7]

Pharmacokinetic properties

After oral administration approximately 80% of an administered dose of fluoxetine is absorbed from the gastrointestinal tract. Fluoxetine is extensively bound to tissue and plasma proteins (95%), which results in a large apparent volume of distribution. Steady-state plasma concentrations are obtained after 4 to 6 weeks of administration. The primary metabolite of fluoxetine is norfluoxetine, which has similar pharmacological activity to that of the parent compound. There is large interpatient variability in fluoxetine clearance which may be due to the existence of polymorphic metabolism. The elimination half-lives of fluoxetine and norfluoxetine after multiple doses of the parent compound range from 2 to 7 days and 7 to 15 days, respectively. Renal function, age or bodyweight do not appear to alter the clearance of fluoxetine; however, in patients with hepatic dysfunction clearance is significantly reduced and the elimination half-life of fluoxetine is prolonged.[7]

Therapeutic potential

Evidence from a number of comparative and noncomparative studies suggests that fluoxetine is an effective agent in the treatment of OCD in dosages of 20 to 80 mg/day. As with other agents used in the treatment of OCD, improvements in symptoms are observed after 4 to 8 weeks of fluoxetine treatment. Two placebo-controlled trials reported decreases in mean total Yale-Brown Obsessive Compulsive Scale scores of 19 to 29% after treatment with fluoxetine 20 to 60 mg/day for 8 and 13 weeks, compared with reductions of 3 and 17%, respectively for placebo-treated patients. A significant difference compared with placebo was reported after 5 weeks of treatment in one of these studies. Response rates ranged from 32 to 48% for fluoxetine-treated patients and were 8 and 26% for placebo treated patients. Studies comparing fluoxetine with clomipramine in the treatment of OCD have included only small numbers of patients and/or have been poorly controlled but indicate that fluoxetine is equal to, or possibly less effective than, clomipramine. A meta-analysis of placebo-controlled clinical trials found fluoxetine to be similar in efficacy to fluvoxamine and sertraline but less effective than

clomipramine. In uncontrolled trials and case reports, fluoxetine has been administered in combination with other agents such as buspirone, lithium, clomipramine and fenfluramine in an attempt to augment response in patients with treatment -refractory OCD. However, the efficacy of these regimens has not been confirmed by controlled clinical trials. Fluoxetine has shown some efficacy in patients with OCD and concurrent depression or Gilles de la Tourette's syndrome and preliminary data suggest it may also be effective in paediatric patients with OCD.[7]

Tolerability and drug interactions

The most commonly reported adverse effects of fluoxetine include nausea, insomnia, headache, nervousness, somnolence, anxiety, anorexia, diarrhoea, dry mouth, tremor and rhinitis. The incidence of adverse effects and rate of treatment discontinuation due to adverse effects tend to be dose-dependent. While data comparing the adverse effects of fluoxetine and other agents in the treatment of OCD are not available, data from studies in the treatment of depression demonstrate that fluoxetine is associated with significantly less sedation and fewer anticholinergic adverse effects (dry mouth, constipation, blurred vision) compared with tricyclic antidepressants. In addition, fluoxetine is associated with minimal cardiovascular effects and is less harmful in overdose than tricyclic antidepressants. However, fluoxetine treatment produces a higher incidence of certain CNS activating (insomnia, anxiety, anorexia) and gastrointestinal (nausea, diarrhoea) adverse effects than tricyclic antidepressants. Fluoxetine does not appear to increase the overall incidence of suicidal ideation (and may decrease the risk in most patients); however, a paradoxical increase in suicidal ideation may occur in rare cases.[7]

Dosage and administration

The recommended starting dosage of fluoxetine in the treatment of OCD is 20 mg/day, generally administered in the morning. The dosage may be gradually increased in 20 mg/day increments up to a maximum of 80 mg/day. Administering doses of 40mg or more on a twice daily schedule may decrease the incidence of adverse effects.[7]

Olanzapine

Olanzapine is a second-generation antipsychotic agent that exhibits a wide array of receptor affinities including 5-$HT_{2A-C,3,6,7}$, dopaminergic D_{1-5}, muscarinic M_{1-5}, α_1-adrenergic and histaminergic H1 receptors. These receptor affinities have been shown to relate to recognized clinical and adverse effects of olanzapine. The primary antimanic and antipsychotic effects are likely regulated by the blockade of dopamine D_2 and serotonin 5-HT_{2A} receptors primarily in the mesolimbic pathway. Olanzapine is relatively nonselective at dopamine receptor subtypes, and it shows selectivity for mesolimbic and neocortical over striatal dopamine tracts. Olanzapine exhibits linear pharmacokinetic properties across the clinical dos-age range of 0.5 to 20 mg. It is well absorbed orally with peak concentrations occurring 4–6 hours after oral administration.[8]

Olanzapine in bipolar depression

The first double-blind, placebo-controlled trial available on an atypical antipsychotic agent in bipolar depression was published. olanzapine was shown to be superior to placebo, although the combination of olanzapine and fluoxetine was significantly greater than the placebo and olanzapine alone. As expected, the size of the antidepressant effect of olanzapine was quite small, even though this study enrolled a large number of patients in order to achieve sufficient statistical significance over placebo. Despite this, it was clearly demonstrated that olanzapine does not worsen bipolar depression, as may occur with other antipsychotics, and it even statistically improved symptoms (although clinically, the effect may not very relevant and limited to sleep, anxiety and appetite items of the depression rating scale). The combination arm with fluoxetine that needed much fewer subjects to demonstrate that it was superior to the other two suggests that olanzapine would behave more like lithium than an antidepressant in the treatment of bipolar depression, with a positive but modest effect in monotherapy and a much clearer effect in combination with antidepressants. It would have been interesting to incorporate a fourth arm with fluoxetine alone in this study, in order to discern the added value of olanzapine in the combination in greater detail. This trial did not show a greater risk than placebo regarding switch risk to mania in any of the groups, although its duration was 8 weeks, a period which is somewhat short to detect possible differences in this aspect. The mean dose of olanzapine in monotherapy drug therapy was ~10 mg/day, whereas when used in combination with fluoxetine, olanzapine 7.5 mg/day and fluoxetine 40 mg/day were used.

However, once again, it is necessary to be cautious when extrapolating the doses used in placebo-controlled trials to the clinical practice, especially in those that do not analyse fixed doses of the drug in question, as is the case. Clinical experience seems to indicate that lower doses are sufficient in the case of depressive phases.[9]

Safety and tolerability

The main problem with regard to tolerability and safety of the drug occurring in these studies was, as predicted, weight gain, which could also be associated to other metabolic complications, such as diabetes mellitus. In fact, the American Association, the American Diabetes association and the FDA have recently raised warnings concerning careful assessment of metabolic and weight gain risks in patients treated with atypical antipsychotics and particularly in the case of olanzapine. However, so far, no-one has demonstrated that this possible complication is exclusive to olanzapine or that it may not be attributed to the underlying disease itself. Weight gain is of particular concern in bipolar patients, due to potential additive effects of treatments and is likely to be a major limitation in the use of olanzapine. In an attempt to minimise weight gain, a successful strategy, at least for 50% of the intended-to-treat patients, has been to combine olanzapine with topiramate. Other perhaps less important side effects of olanzapine are somnolence and, at high doses, extrapyramidal symptoms.[9]

Olanzapine-fluoxetine combination (OFC) therapy

Olanzapine-fluoxetine combination (OFC) therapy and quetiapine are the only FDA approved medications for the treatment of acute bipolar depression. There is some evidence to suggest that olanzapine monotherapy may have some efficacy in depression, though it is clearly less effective than the combination therapy, based on current reported research studies. In a study by Tohen, Vieta *et al* (2003), the efficacy of olanzapine and OFC therapy were compared to placebo in the treatment of bipolar I depression. The results of the study revealed that both olanzapine monotherapy and OFC were significantly more effective than placebo from week 4 to week 8 in decreasing symptoms of depression and producing response and remission. The limitations of this study included a higher attrition rate and the lack of a fluoxetine monotherapy comparison arm. However, this was the first placebo-controlled trial comparing an antipsychotic or mood-stabilizing agent alone and in combination with an antidepressant agent

with the combination demonstrating a robust antidepressant effect with a lower risk of switching to mania. The study had lower rates of discontinuation due to adverse events with improved response and remission rates.[8]

Divalproex

Divalproex is the most commonly prescribed anticonvulsant medication for patients with bipolar disorders, with prescription rates similar to lithium. Divalproex has demonstrated efficacy in preventing depressive episodes during maintenance treatment, but it is not routinely prescribed for the treatment of acute bipolar disorders depression, and there is a perception among clinicians that there is little evidence to support its use.[10]

Clinical trials

In double-blind, placebo-controlled, clinical trials of divalproex, the patients suffering from bipolar I depression treated with divalproex showed greater improvement in symptoms of depression and anxiety than those treated with placebo. The rate of improvement over time in patients treated with divalproex was about twice as great for symptoms of depression and about three times as great for symptoms of anxiety versus placebo. Divalproex was well tolerated in this group with only one patient in the divalproex-treated group withdrawing due to adverse effects related to medication. Also, one patient in the divalproex group was discontinued from the study due to symptoms of mania, while two patients in the placebo group were discontinued due to symptoms of mania. Three patients receiving divalproex were discontinued due to nonresponse. However, for the group as a whole, there was no substantial worsening of symptoms of depression, suggesting that divalproex does not routinely induce or worsen depression. In a previous open trial of divalproex for unipolar major depressive disorder, most patients significantly improved during an 8-week trial, and no patient worsened. Thus, divalproex can probably be safely used without risk of worsening the depressive symptoms.[11]

Efficacy in mania

The two studies leading to Food & Drug Administration (FDA) approval of divalproex for treatment of mania were randomized, double-blind, placebo-controlled, 3-week trials in hospitalized patients. The single-centre study by Pope et al. enrolled patients either non-responsive or intolerant to lithium. The larger study, conducted at eight academic centres,

enrolled patients regardless of previous treatment with, or response to lithium, and included an active comparator group of patients randomized to lithium. The study is the only randomized, placebo-controlled study of lithium in mania, and the largest placebo-controlled study of lithium in mania. The studies excluded patients with mania associated with substance abuse or other medical disorders. Modest amounts of lorazepam or chloral hydrate were allowed in the first portion of the studies. In both studies, rates of response to divalproex were approximately twice that of response to placebo. Both studies indicated onset of improvement within the first week of treatment, and, in the study with a lithium comparator, somewhat earlier improvement with divalproex than with lithium. On the primary overall outcome measure, change from baseline in the 10-item Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia (SADS), modified to include an item on impaired insight, divalproex and lithium were equivalent in efficacy. Divalproex was more effective than lithium among patients with depressive mania, defined as mania associated with two or more pure depressive symptoms.[12]

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Survey Form

1) In your clinical practice, what is the percentage of patients with bipolar disorder?

A. <10%
B. 10-20%
C. 20-30%
D. >40%

2) According to published evidences, Olanzapine and Fluoxetine combination is first line of treatment option for acute bipolar disorder. Do you agree?

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

3) How do you rate Olanzapine and Fluoxetine combination therapy in the management bipolar disorder in terms of safety?

A. Excellent
B. Good
C. Average
D. Poor

4) How do you rate Olanzapine and Fluoxetine combination therapy in the management bipolar disorder in terms of efficacy?

A. Excellent
B. Good
C. Average
D. Poor

5) In your opinion, how is the tolerability of Olanzapine and Fluoxetine combination?

A. Excellent
B. Good
C. Average
D. Poor

6) **In your clinical practice, what is the percentage of patients with treatment resistant depression?**

A. <10%
B. 10-20%
C. 20-30%
D. >40%

7) **According to published evidences, in treatment resistant depression, Olanzapine and Fluoxetine combination therapy offers higher remission and response rate than monotherapy. Do you agree?**

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

8) **Both lithium and divalproex were adequately tolerated and efficacious in the treatment of mania in patients with bipolar disorder.**

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

9) **How do you rate divalproex therapy in the management bipolar disorder in terms of efficacy?**

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

10) How do you rate divalproex therapy in the management bipolar disorder in terms of safety?

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

11) In your clinical practice, what is the percentage of patients with panic disorder?

A. <10%
B. 10-20%
C. 20-30%
D. >40%

12) According to published evidences, Paroxetine is first line of treatment option for panic disorder. Do you agree?

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree

13) How do you rate Paroxetine therapy in the management panic disorder in terms of safety?

A. Excellent
B. Good
C. Average
D. Poor

14) How do you rate Paroxetine therapy in the management panic disorder in terms of efficacy?

A. Excellent
B. Good
C. Average
D. Poor

15) In your opinion, how is the tolerability of Paroxetine in the management panic disorder?

A. Excellent
B. Good
C. Average
D. Poor

Survey Findings

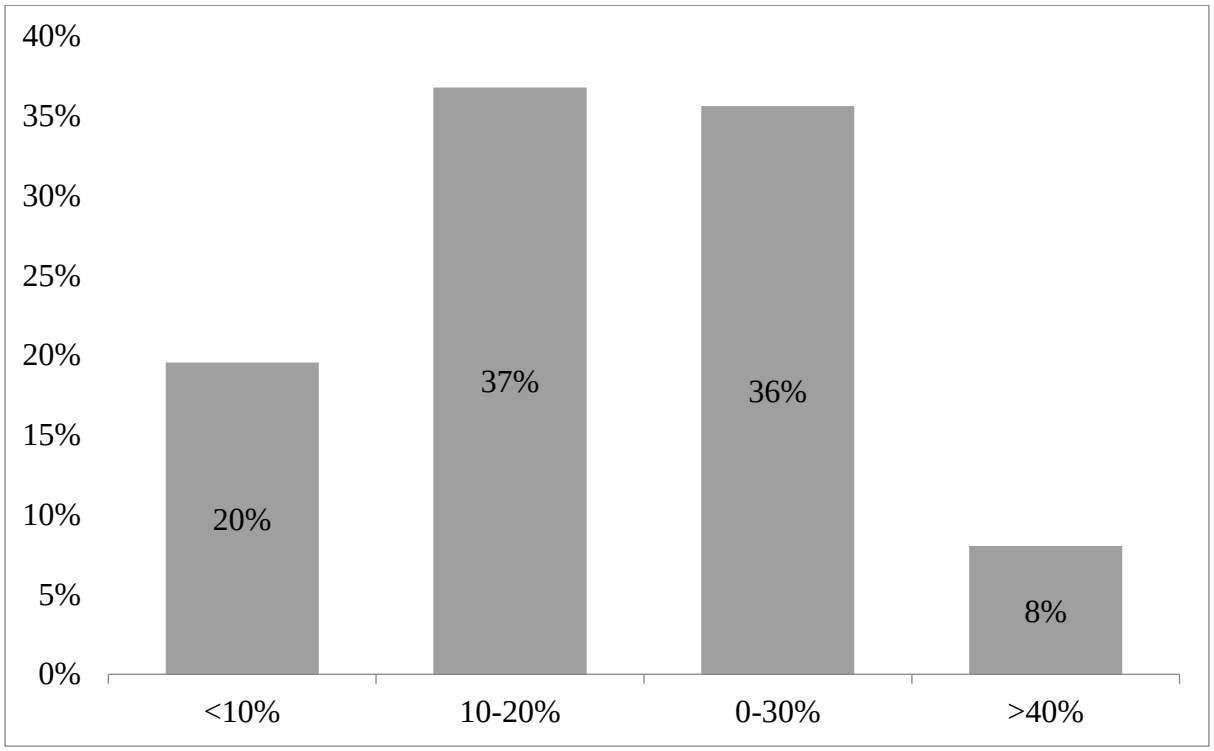
1) In your clinical practice, what is the percentage of patients with bipolar disorder?

A. <10%

B. 10-20%

C. 20-30%

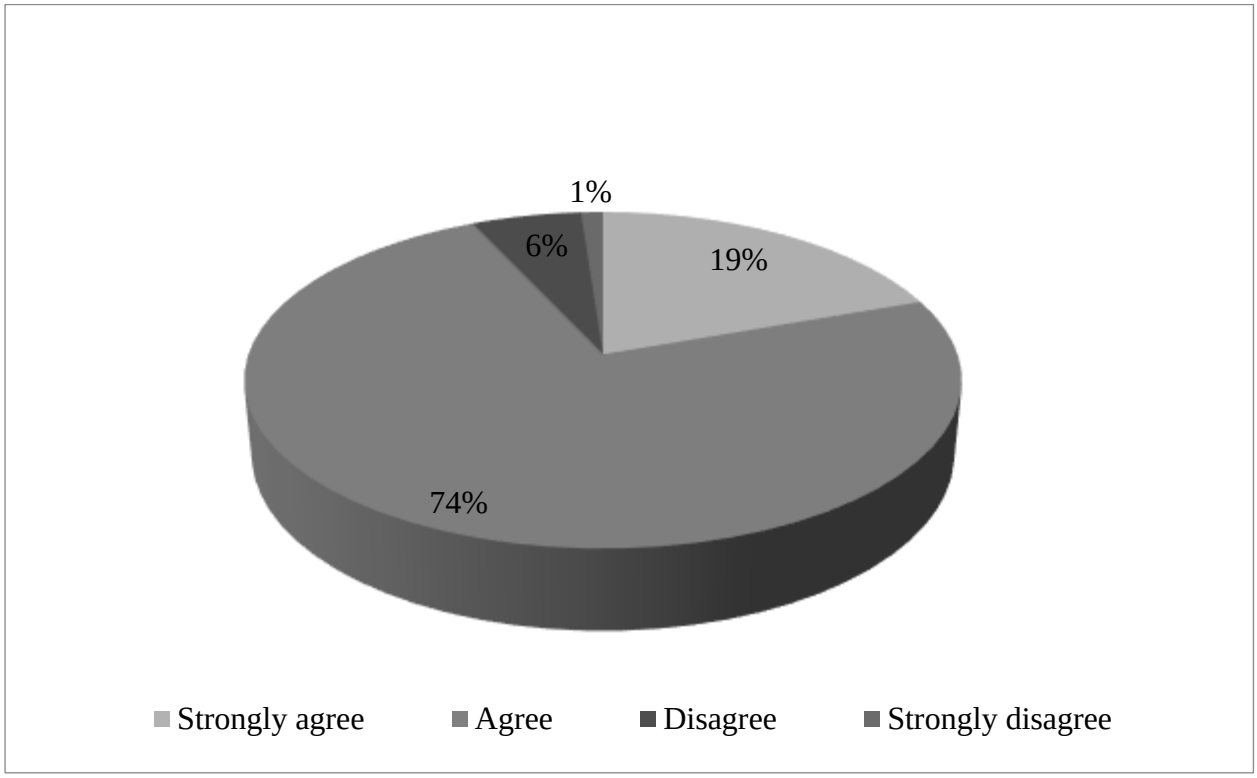
D. >40%



According to 37% of doctors, the percentage of patients with bipolar disorder is 10-20%.

2) According to published evidences, Olanzapine and Fluoxetine combination is first line of treatment option for acute bipolar disorder. Do you agree?

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



A majority of doctors, 74%, agree that Olanzapine and Fluoxetine combination is first line of treatment option for acute bipolar disorder.

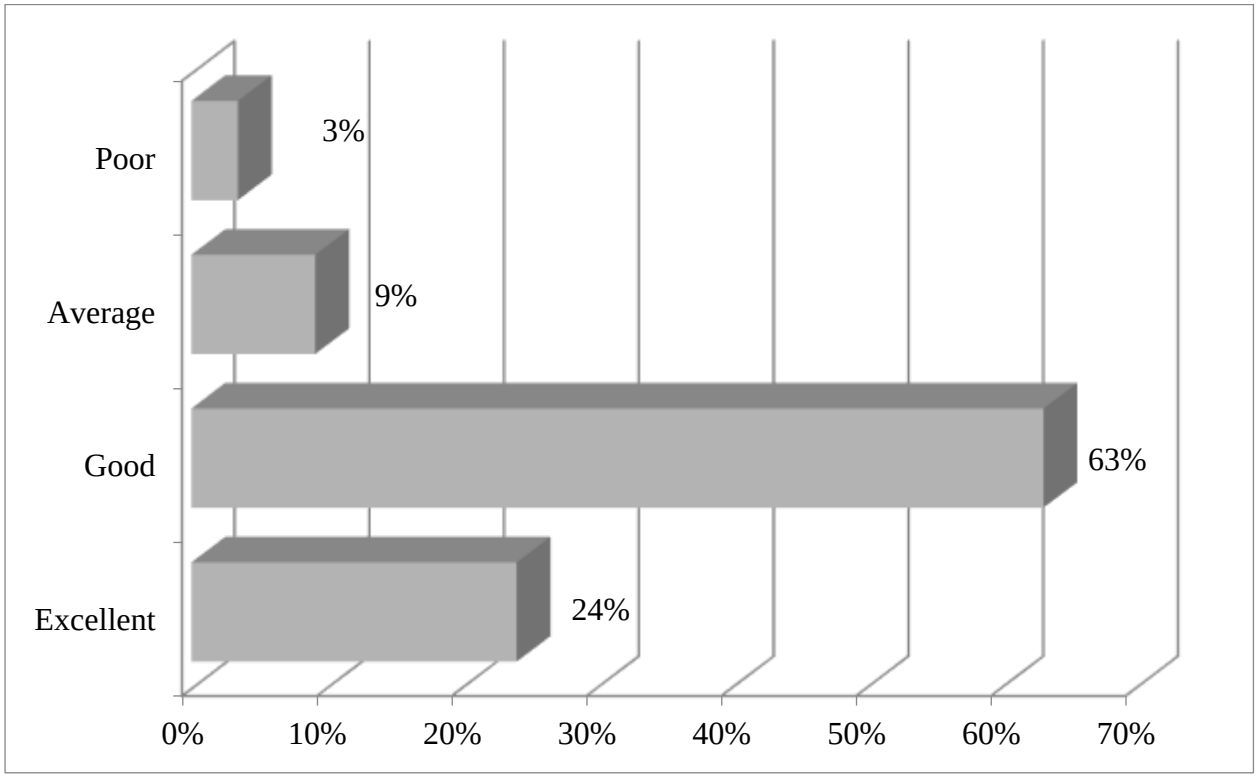
3) How do you rate Olanzapine and Fluoxetine combination therapy in the management bipolar disorder in terms of safety?

A. Excellent

B. Good

C. Average

D. Poor



According to 63% of doctors, the combination therapy of Olanzapine and Fluoxetine was rated as good in terms of safety for managing bipolar disorder.

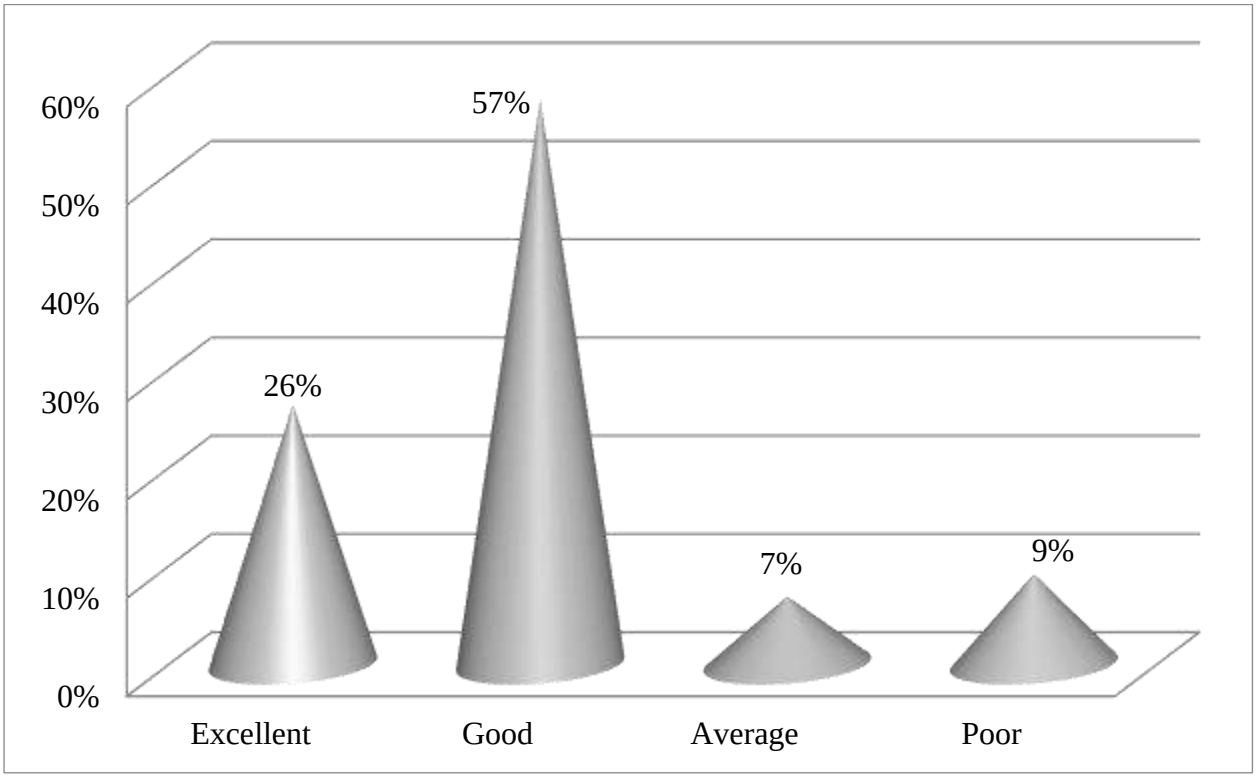
4) How do you rate Olanzapine and Fluoxetine combination therapy in the management bipolar disorder in terms of efficacy?

A. Excellent

B. Good

C. Average

D. Poor



As per 57% of doctors, the combination therapy of Olanzapine and Fluoxetine was rated as good in terms of efficacy for managing bipolar disorder.

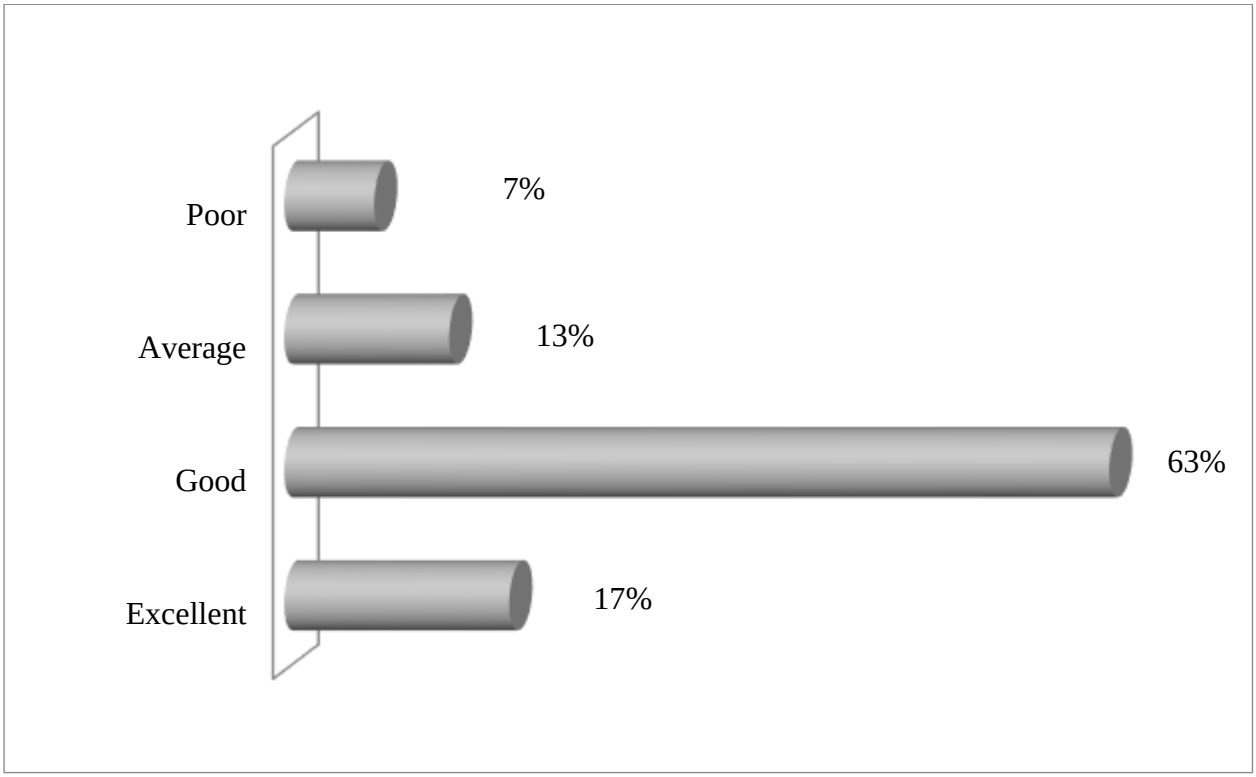
5) In your opinion, how is the tolerability of Olanzapine and Fluoxetine combination?

A. Excellent

B. Good

C. Average

D. Poor



A majority of 63% of doctors, mentioned that the tolerability of Olanzapine and Fluoxetine combination is good.

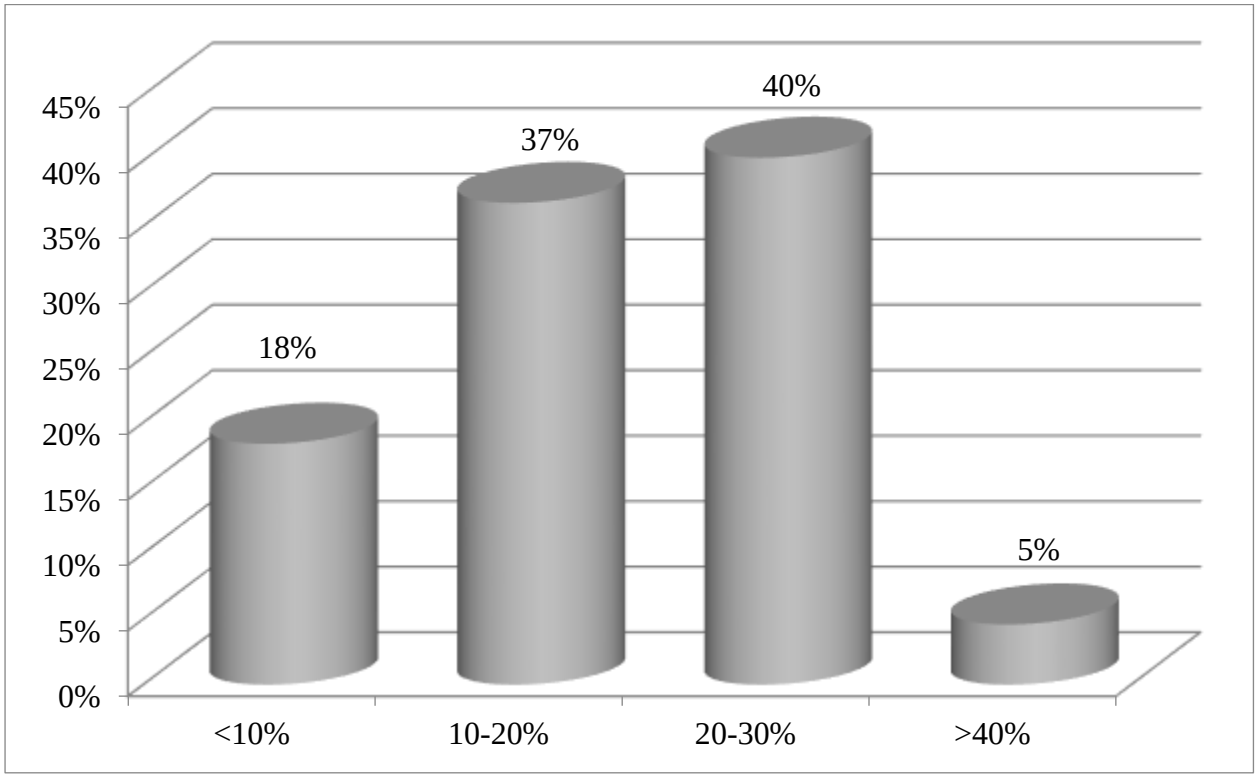
6) In your clinical practice, what is the percentage of patients with treatment resistant depression?

A. <10%

B. 10-20%

C. 20-30%

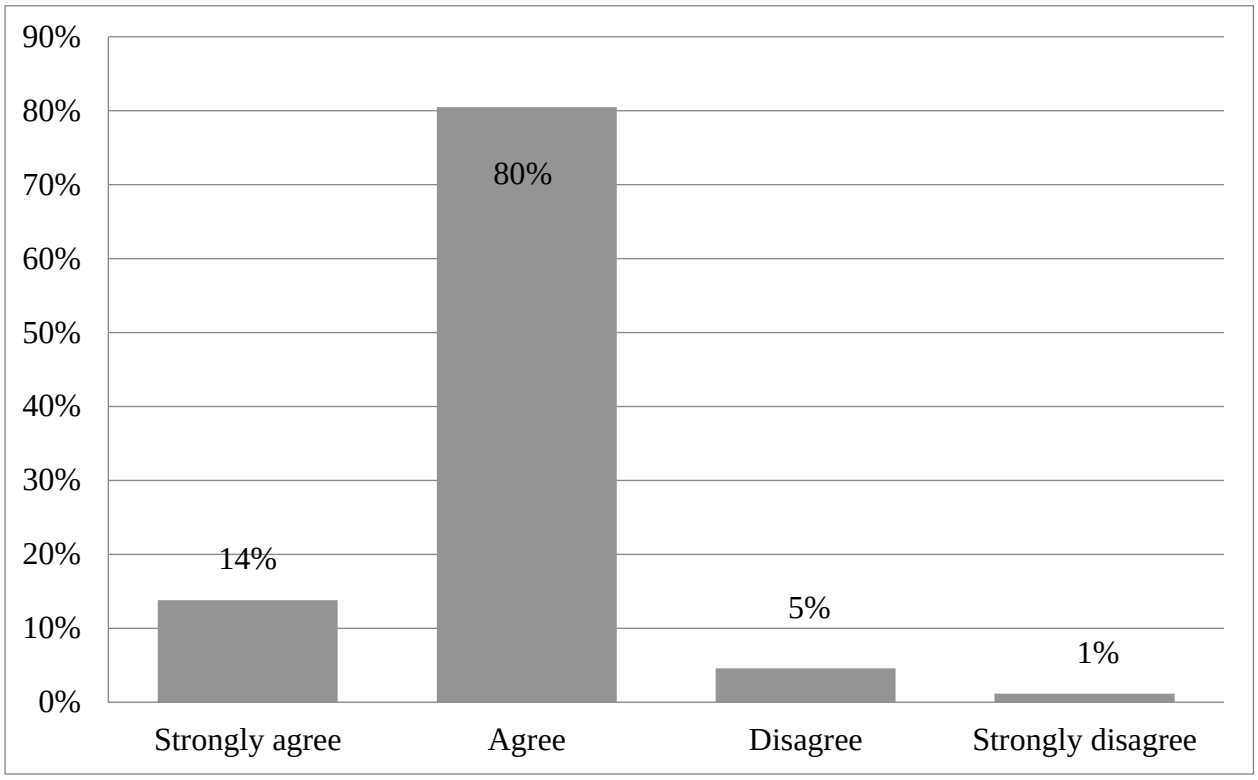
D. >40%



Around 40% of doctors, the percentage of patients with treatment resistant depression is 20-30%.

7) According to published evidences, in treatment resistant depression, Olanzapine and Fluoxetine combination therapy offers higher remission and response rate than monotherapy. Do you agree?

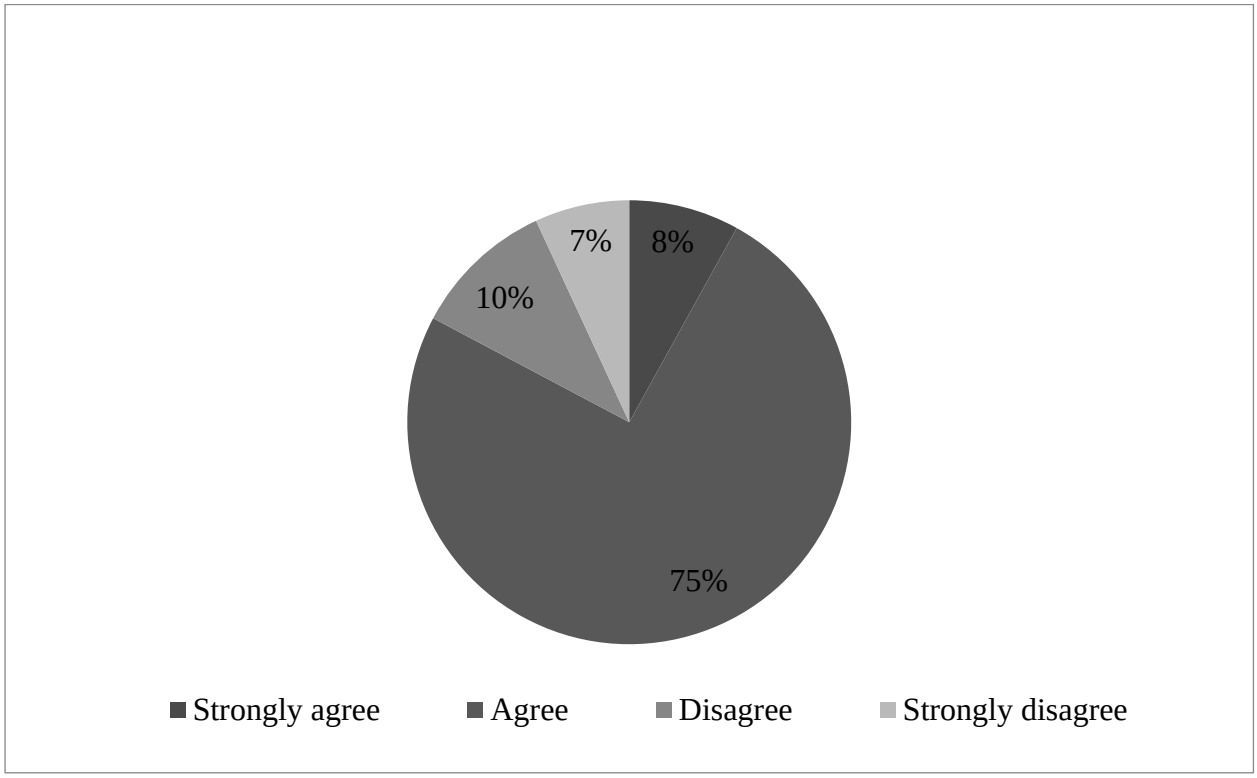
A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



80% of doctors agree that, according to published evidence, in treatment-resistant depression, Olanzapine and Fluoxetine combination therapy offers higher remission and response rates than monotherapy.

8) Both lithium and divalproex were adequately tolerated and efficacious in the treatment of mania in patients with bipolar disorder.

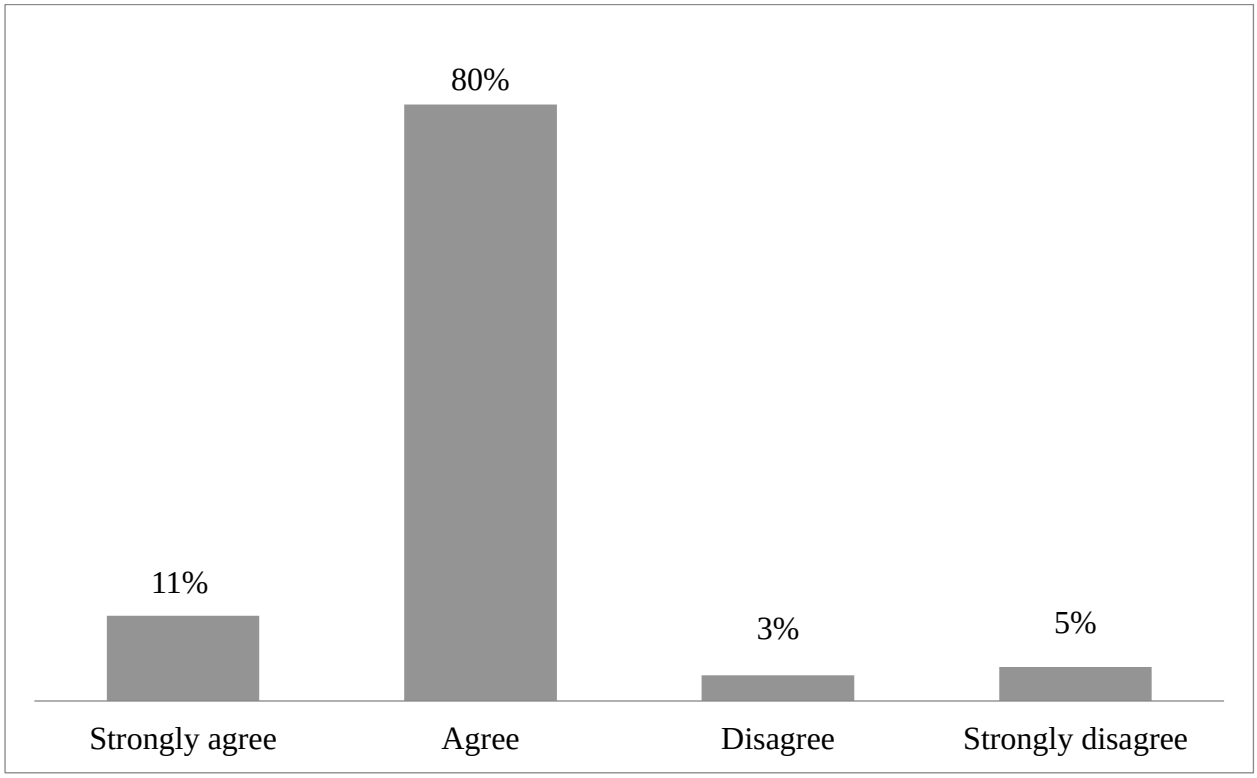
A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



A majority of doctor, 75%, agree that both lithium and divalproex were adequately tolerated and efficacious in treating mania in patients with bipolar disorder.

9) How do you rate divalproex therapy in the management bipolar disorder in terms of efficacy?

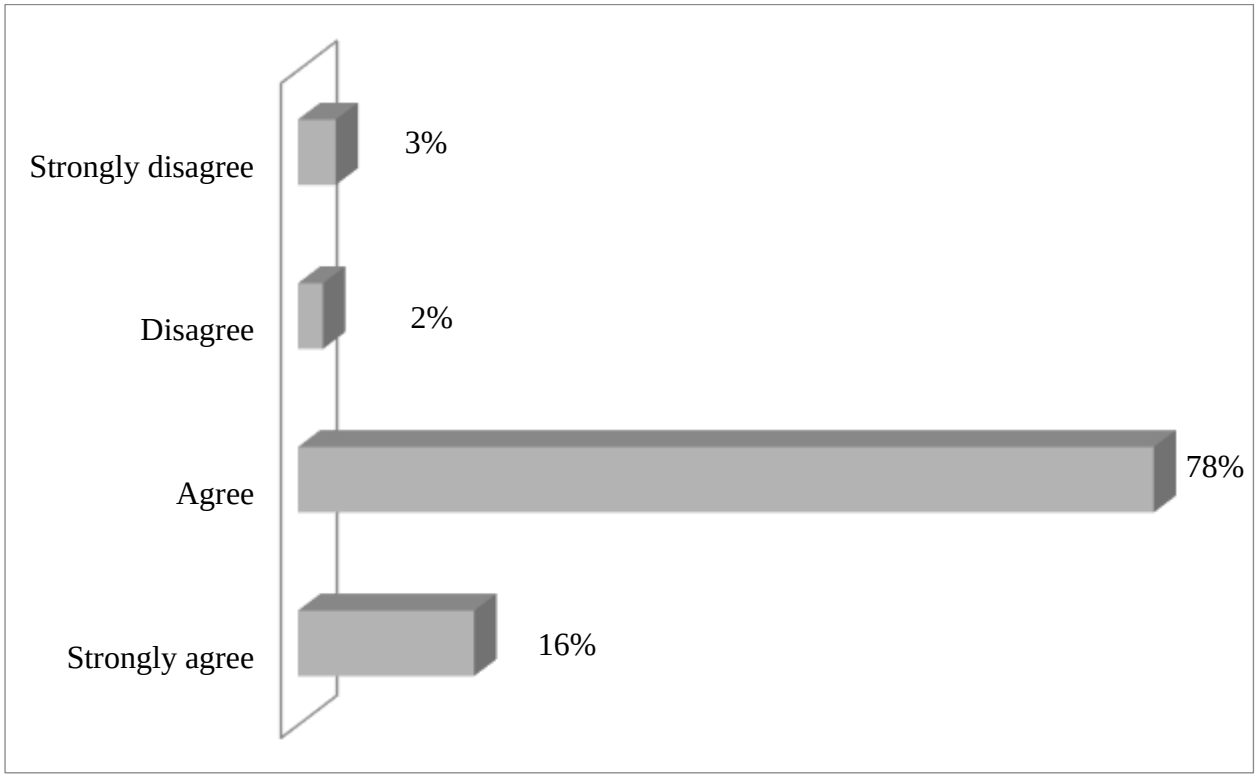
A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



Around 80% of doctors, agree with the efficacy of divalproex therapy in managing bipolar disorder.

10) How do you rate divalproex therapy in the management bipolar disorder in terms of safety?

A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



Around 78% of doctors, agree with the safety of divalproex therapy in managing bipolar disorder.

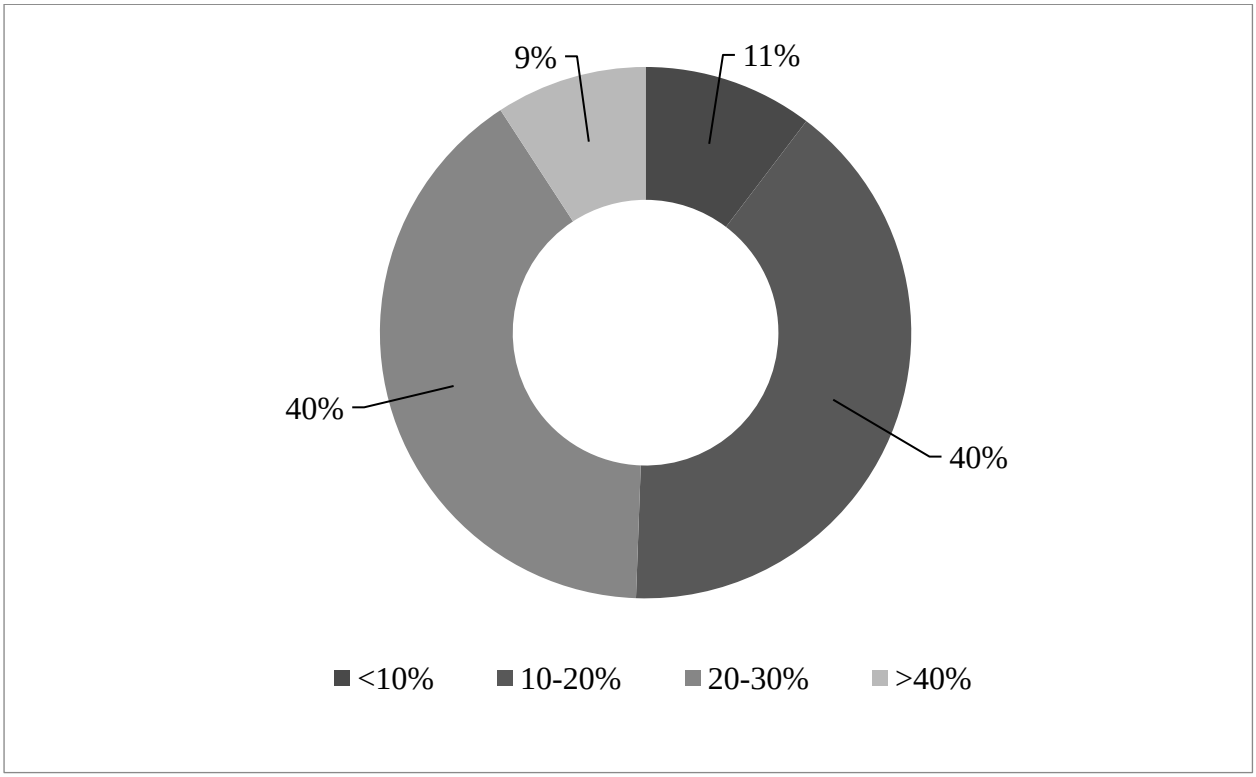
11) In your clinical practice, what is the percentage of patients with panic disorder?

A. <10%

B. 10-20%

C. 20-30%

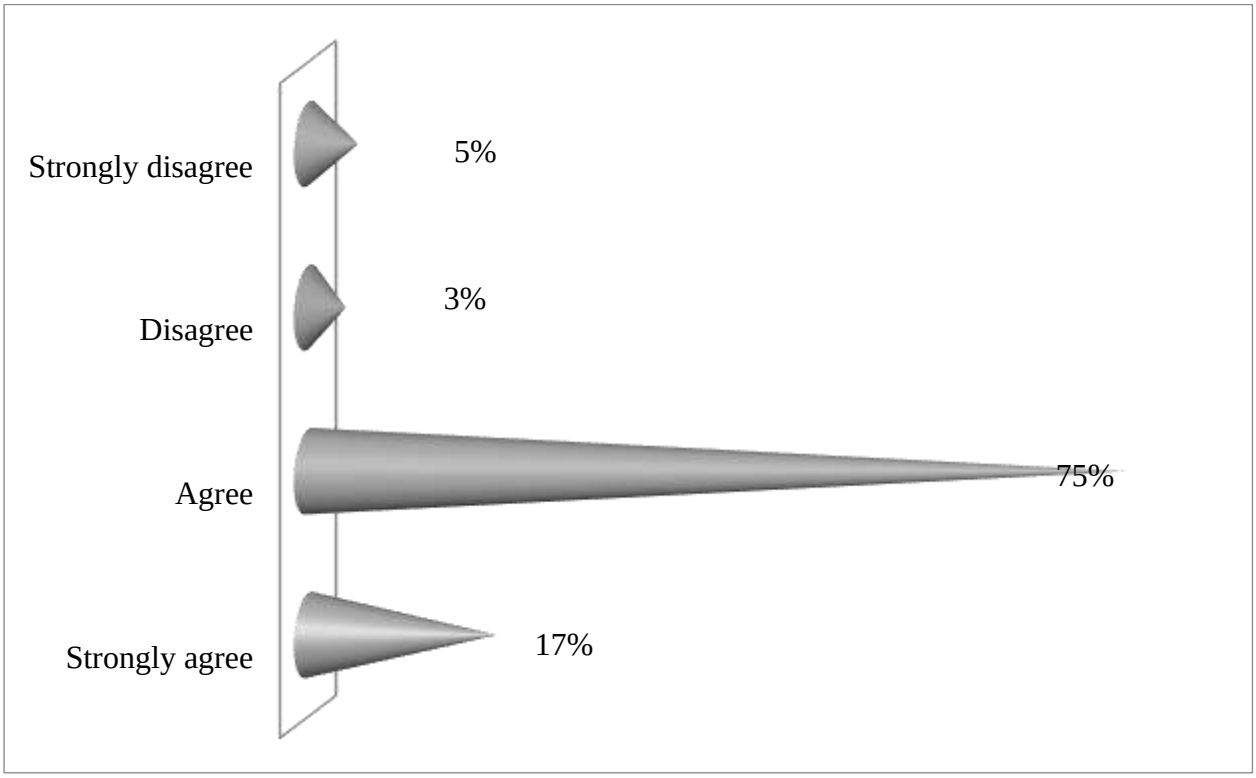
D. >40%



According to 40% of doctors, the percentage of patients with panic disorder in their clinical practice ranges from 10-20%, while another 40% reported it to be between 20-30%.

12) According to published evidences, Paroxetine is first line of treatment option for panic disorder. Do you agree?

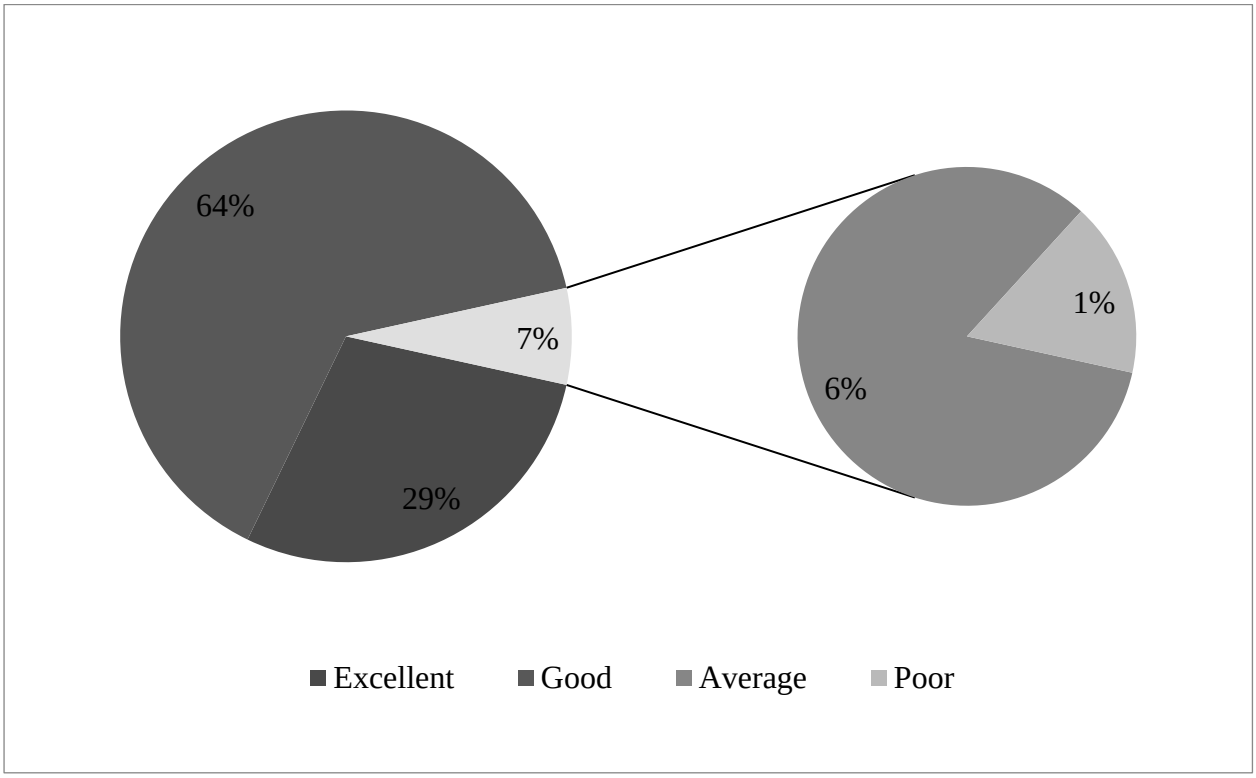
A. Strongly agree
B. Agree
C. Disagree
D. Strongly disagree



75% of doctors agree that, according to published evidence, Paroxetine is first line of treatment option for panic disorder.

13) How do you rate Paroxetine therapy in the management panic disorder in terms of safety?

A. Excellent
B. Good
C. Average
D. Poor



As per 64% of doctors, the Paroxetine therapy was rated as good in terms of safety for managing panic disorder.

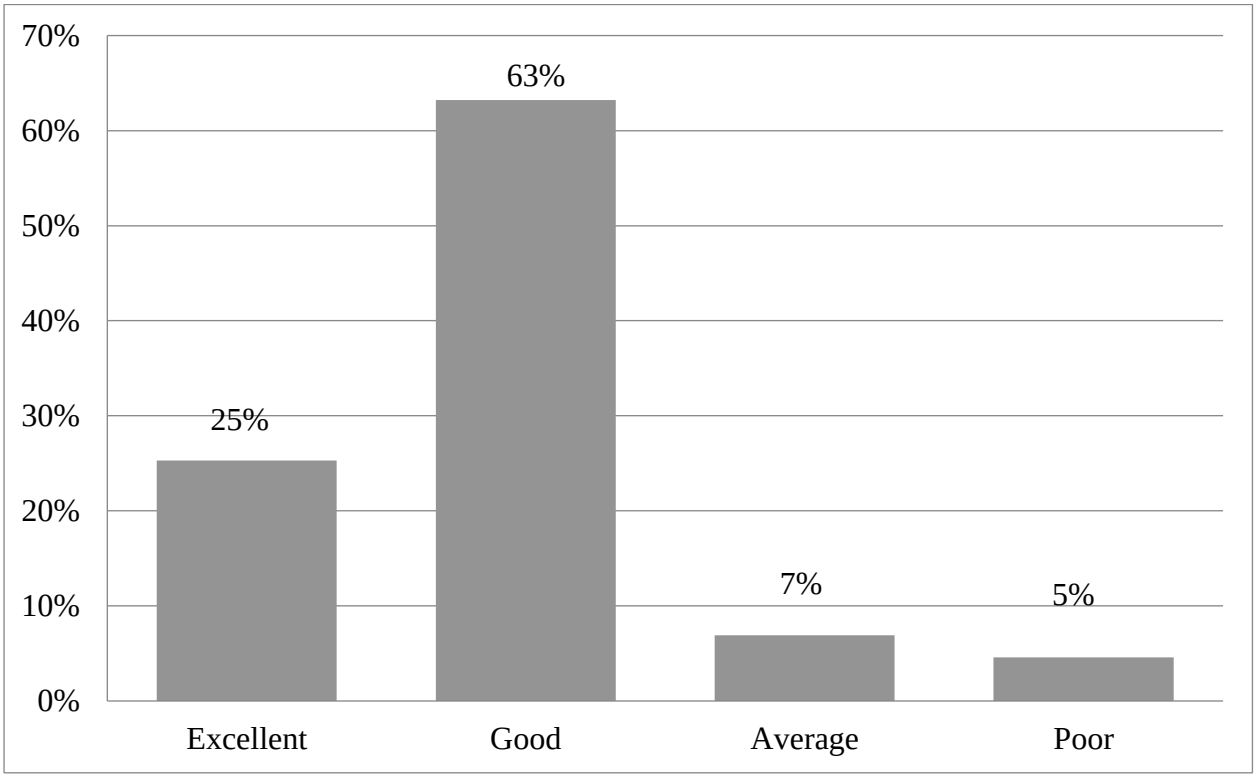
14) How do you rate Paroxetine therapy in the management panic disorder in terms of efficacy?

A. Excellent

B. Good

C. Average

D. Poor



As per 63% of doctors, the Paroxetine therapy was rated as good in terms of efficacy for managing panic disorder.

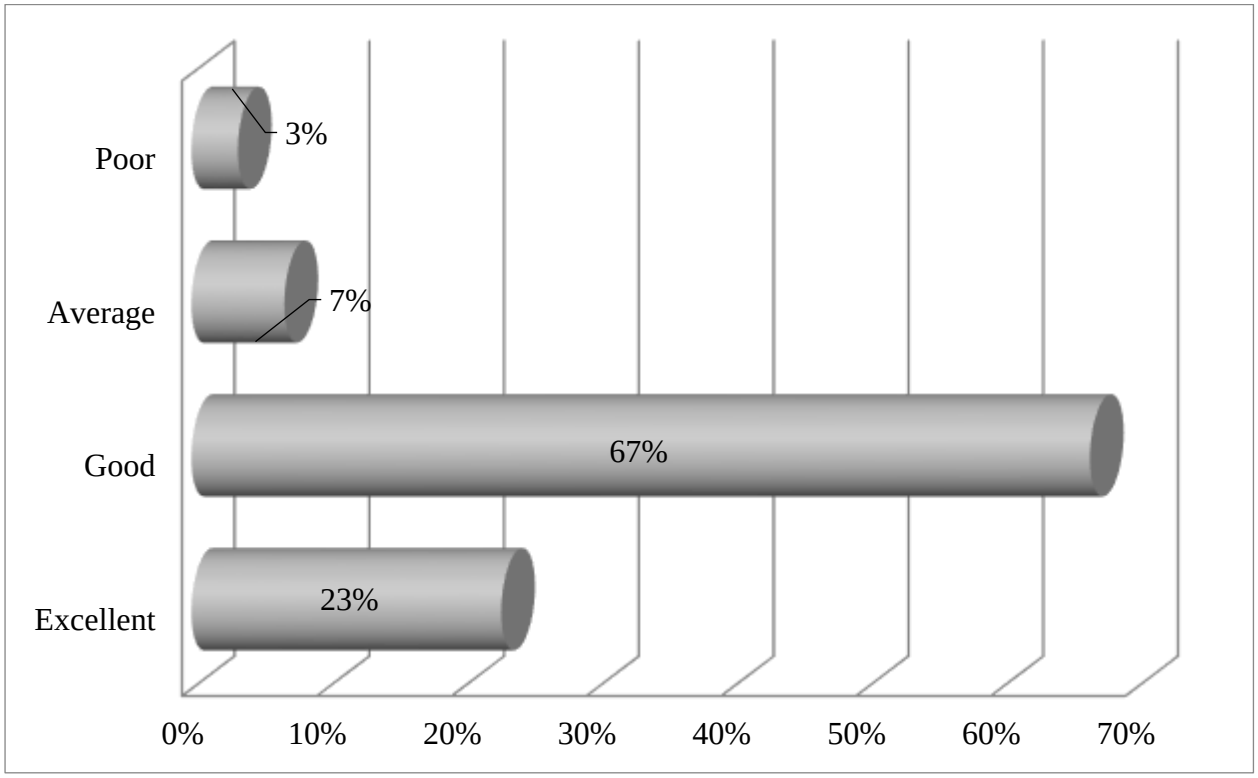
15) In your opinion, how is the tolerability of Paroxetine in the management panic disorder?

A. Excellent

B. Good

C. Average

D. Poor



According majority of doctors, 67%, the tolerability of Paroxetine therapy is good in managing panic disorder.

Summary

- According to 37% of doctors, the percentage of patients with bipolar disorder is 10-20%.
- A majority of doctors, 74%, agree that Olanzapine and Fluoxetine combination is first line of treatment option for acute bipolar disorder.
- According to 63% of doctors, the combination therapy of Olanzapine and Fluoxetine was rated as good in terms of safety for managing bipolar disorder.
- As per 57% of doctors, the combination therapy of Olanzapine and Fluoxetine was rated as good in terms of efficacy for managing bipolar disorder.
- A majority of 63% of doctors, mentioned that the tolerability of Olanzapine and Fluoxetine combination is good.
- Around 40% of doctors, the percentage of patients with treatment resistant depression is 20-30%.
- 80% of doctors agree that, according to published evidence, in treatment-resistant depression, Olanzapine and Fluoxetine combination therapy offers higher remission and response rates than monotherapy.
- A majority of doctor, 75%, agree that both lithium and divalproex were adequately tolerated and efficacious in treating mania in patients with bipolar disorder.
- Around 80% of doctors, agree with the efficacy of divalproex therapy in managing bipolar disorder.
- Around 78% of doctors, agree with the safety of divalproex therapy in managing bipolar disorder.
- According to 40% of doctors, the percentage of patients with panic disorder in their clinical practice ranges from 10-20%, while another 40% reported it to be between 20-30%.
- 75% of doctors agree that, according to published evidence, Paroxetine is first line of treatment option for panic disorder.
- As per 64% of doctors, the Paroxetine therapy was rated as good in terms of safety for managing panic disorder.
- As per 63% of doctors, the Paroxetine therapy was rated as good in terms of efficacy for managing panic disorder.
- According majority of doctors, 67%, the tolerability of Paroxetine therapy is good in managing panic disorder.

Market opportunities

The market for pharmacologic interventions to address bipolar and panic disorders, including medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex, presents significant opportunities for pharmaceutical companies to develop and market effective treatments.

Value for healthcare professionals

Healthcare professionals recognize the efficacy of medications such as Paroxetine, Fluoxetine, Olanzapine, and Divalproex in managing bipolar and panic disorders, indicating the value of these treatments in clinical practice.

Adverse effect management

Considering the potential adverse effects associated with long-term use of medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex, there may be opportunities for pharmaceutical companies to focus on minimizing these effects, such as fatigue, dizziness, and weight gain.

Withdrawal management

The need for strategies to manage withdrawal and transition to alternative treatments, particularly with medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex, underscores the importance of ensuring continuity of care and optimal patient outcomes.

Market positioning

Pharmaceutical companies can position medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex as preferred options for the treatment of bipolar and panic disorders, highlighting their efficacy, tolerability, and potential benefits in patients with varying symptom profiles and comorbidities.

Personalized treatment decisions

The preference for specific medications and the consideration of clinical benefits in patients with bipolar and panic disorders underscore the importance of personalized treatment decisions tailored to individual patient characteristics and needs.

Improving patient outcomes

Continued research and development efforts focusing on optimizing dosing regimens, improving efficacy, and minimizing adverse effects of medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex can contribute to better patient outcomes and overall management of bipolar and panic disorders. Additionally, education initiatives targeting healthcare professionals can enhance awareness and understanding of the clinical benefits of these medications in bipolar and panic disorder management.

In summary, the analysis highlights the importance of medications like Paroxetine, Fluoxetine, Olanzapine, and Divalproex in managing bipolar and panic disorders. Pharmaceutical companies can leverage this opportunity by developing and marketing innovative treatments that address the specific needs and preferences of healthcare professionals and patients, ultimately improving patient care and outcomes in the management of these conditions.

Notes

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Weston Medical Education Foundation of India
Office No:- 99,9th Floor, Kalpataru Avenue, Opp. ESIC Hospital, Kandivali (East) , Mumbai -400101.
M: 9920154297 | W: www.wmefi.co.in