Review Article

Journal of Pharmaceutics and Therapeutics

Current Strategies of Quetiapine Fumarate Delivery in Management of Bipolar Disorder and Schizophrenia

Patil D^{1,*}, Paliwal S¹, Sharma S¹, Pattewar S² and Singh G³

¹Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India

²Sanjivani Institute of Pharmacy and Research, Kopargaon, India

³Raja Balwant Singh Engineering Technical Campus, Bichpuri, Agra, India

***Correspondence:** Deepak Patil, Department of Pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan-304 022, India, E-mail: dnp_pharma@rediffmail.com

Received: January 18, 2019; Accepted: February 19, 2019; Published: February 25, 2019

Abstract

Bipolar disorder is psychological illness with periodic episodes of mania and depression. Schizophrenia is a complex mental disorder identified by delusions, hallucinations, disorganized behavior, impaired cognitive ability, disorganized speech and sudden change in personality. In both the diseases quetiapine fumarate (QF) drug is worth important in today's scenario. This review gives complete QF drug profile along with mechanism of action. Quetiapine alone is successful for acute bipolar depression and the prevention of mania/hypomania switching. Literature survey section of this review gives information about quetiapine in different dosage form. By this review one can explore the scale up of quetiapine fumarate not only with immediate release and sustained release dosage form but also with novel drug delivery system like solid lipid nanoparticle and nanostructured lipid carrier.

Keywords: Bipolar disorder, Delusions, Hallucinations, Schizophrenia, Quetiapine fumarate

Abbreviation: BCS: Biopharmaceutical Classification System; D: Dopamine; DSC: Differential Scanning Colorimetric; EF: Entrapment Efficiency; H: Histamine; HD: High Dose; HPMC: Hydroxy Propyl Methyl Cellulose; HT: Hydroxy Tryptamine; IR: Immediate Release; LD: Low Dose; NRI: Noradrenaline Reuptake Inhibitor; QF: Quetiapine Fumarate; QFSLN: Quetiapine Fumarate loaded Solid Lipid Nanoparticles; SEM: Scanning Electron Microscopy; SLN: Solid Lipid Nanoparticles; SMEDDS: Self Microemulsifying Drug Delivery Systems; SNEDDS: Self Nanoemulsifying Drug Delivery System; UK: United Kingdom; US: United States; XR: Extended Release; α : Adrenergic

Introduction

Approximately 2-4% of the general population suffers from bipolar I, bipolar II [1]. In 2015, an estimated 17,000 people in world died by schizophrenia. In both the diseases quetiapine fumarate (QF) drug is worth important in today's scenario. It is available in traditional dosage form, by this review we want to explore different dosage form for QF.

Bipolar disorder (manic depression) is psychological

illness with periodic episodes of mania and depression. Patient with bipolar disorder feels major changes in sleep, energy, thinking, behavior and highs and lows as two 'poles' of mood, so the name 'bipolar disorder'. In between those poles, patient feels normal.

Sometimes patient with bipolar disorder feels over excitement and confidence (manic episode) along with irritability, reckless decision-making, hallucinations. The term 'Hypomania' describes milder symptoms of mania without delusions or hallucinations. Sometimes

patient with bipolar disorder feels very sad or depressed (depressive episode).

Pathophysiology of bipolar disorder includes G protein subunits abnormality. There are elevated levels of the stimulatory G protein (Gas) and post-receptor stimulated adenylyl cyclase activity [2-4]. Protein kinase C activity [5] and intracellular Ca2+ levels in platelets, lymphocytes and neutrophils also increases in bipolar disorder [6].

Symptoms of (highs) behavior include excessive excitement, sudden changes of mood, restlessness, less concentration, less need for sleep. Symptoms of (lows) behavior include sadness, loss of energy, feelings of worthlessness, uncontrollable crying, need more sleep, changes in appetite and thoughts of suicide [7]. Genes, brain changes, and stress contribute to develop bipolar disorder mostly in late adolescence age. Women are more receptive than men for ‘rapid cycling’ of mood episodes.

What is bipolar I and bipolar II disorder?

Diagnosis of bipolar disorder is crucial task for psychiatrist. Close friends and family member can help the psychiatrist to distinguish bipolar disorder from other psychological disorders that causes change in thinking, mood and behavior (Table 1).

Table 1: Bipolar I and Bipolar II disorder.

Bipolar I	Bipolar II
Patient has episodes of mania and depression	Patient has episodes of hypomania and depression.
Patients are not in neutral state or functions normally.	Patients also in neutral state or functions normally.
Bipolar I is mainly associated with mania.	Bipolar II is mainly associated with depressive state.
Symptoms are talkative-ness, increased grandilo-quence, less need for sleep, increase in energy level, racing thoughts and poor attention	Symptoms are depressed mood, changes in sleep and eating habits, ab-sence of energy, feelings of guilt and restlessness, and suicidal thoughts [8].

Treatment for bipolar disorder includes drugs such as carbamazepine, lamotrigine, lithium or valproate. Sometimes drugs such as olanzapine, quetiapine, lurasidone and cariprazine and antidepressants are also used. Combinations of above mood stabilizers and antipsychotic drugs are often used along with patient counseling [9].

Schizophrenia

Schizophrenia is a complex mental disorder identified by delusions, hallucinations, impaired cognitive ability [10,11], disorganized speech [12], and sudden change in personality and behavior [13]. Pathophysiology include over or deficiency dopamine, serotonin and glutamate, with imbalance in levels of aspartate, glycine and gamma-aminobutyric acid.

Positive symptoms of schizophrenia include repetition of certain motions again and again (stereotypies), moving or talking for a while (catatonia). Negative symptoms include talking in a low voice, expressionless face, stick to an activity. Cognitive symptoms include difficulty in making decisions and less attention [13].

Etiology of schizophrenia includes obstetric difficulties such as bleeding, infections, excessive stress during pregnancy, gestational diabetes, emergency cesarean, deprived of oxygen condition, fetal disturbances during the second trimester and low birth weight [14,15,16].

Schizophrenia can be diagnosed through careful examination of patient’s duration of illness, time of delusions or hallucinations and severity of symptoms [13,17].

Treatment includes first-line monotherapy with second-generation antipsychotic drugs. Next step consists of monotherapy with either other first or second generation antipsychotics antipsychotic drugs. Still no response next step is clozapine monotherapy, if agranulocytosis occurs, clozapine must be discontinued and start with combination therapy of clozapine with first and second generation antipsychotic drugs or electroconvulsive therapy. Still treatment shows no response then monotherapy with first generation antipsychotic drugs along with second generation antipsychotics that has not been tried should be given. Final stage consists of combination therapy of first, second generation antipsychotics, electroconvulsive therapy and/or a mood stabilizer [18].

Quetiapine fumarate (QF)

The combination therapy of olanzapine and fluoxetine was the first treatment which receive regulatory approval in the US for bipolar I depression. Quetiapine was the second medication to be approved for this indication. Doses of quetiapine such as 300 mg and 600 mg once daily at bedtime was effective for bipolar I and bipolar II depression [19].

QF is a second-generation atypical antipsychotic drug, marketed as immediate release tablets (IR) or extended release (XR) tablets. QF is a dibenzothiazepine derivative with biopharmaceutical classification system (BCS) class II drug. Quetiapine and quetiapine XR are approved for schizophrenia, and bipolar disorder in the UK and US. In US quetiapine alone or combination of lithium/ valproate semisodium was approved. Quetiapine XR along with antidepressants is also approved in the UK and US as combination therapy in patients with major depressive disorder who have not showed response to quetiapine monotherapy [20]. Presently, quetiapine is also suggested as front-line treatment for acute bipolar depression [21,22].

Pharmacokinetic profile

The therapeutic dose of quetiapine show linear kinetics with half-life of about 7 hours and low oral bioavailability (7-9%) due to high first-pass metabolism. The T_{max} is 5 hours for XR and 2 hours for IR. Quetiapine XR tablet required to take once daily as high plasma levels are sustained, as opposed to IR required to take at least two times daily.

Quetiapine is metabolized by liver and only 1% excreted unaltered in the urine. In the cytochrome P450 system quetiapine reacts with isoenzymes CYP 3A4 to produce N-desalkyl quetiapine or norquetiapine as key metabolite. Insignificant metabolism occurs through CYP2D6 into 7-hydroxy quetiapine which is inactive metabolite. Both quetiapine and norquetiapine involves for the broad spectrum activity due to action on dopaminergic, serotonergic and noradrenergic receptor [23].

Pharmacodynamic profile

Quetiapine is an antagonist at serotonin 5-hydroxytryptamine 5-HT_{1A} (prefrontal cortex of brain), D₂(dopamine), H₁(histamine), α_1 and α_2 (adrenergic) receptors. Quetiapine has ability to occupy about 30% of D₂ receptors at therapeutic doses. According to 'kiss and run' hypothesis, quetiapine has fast dissociation from D₂ receptors due to which higher doses of quetiapine required to induce its antipsychotic effect. Quetiapine has high attraction for 5-HT_{2A} than for D₂ receptors. Norquetiapine has 5HT₇, 5HT_{2C} and α_2 antagonism, 5HT_{1A} agonism and is also a Noradrenaline Reuptake Inhibitor (NRI) which brings about antidepressant action [19,20,24] (Figure 1).

Figure 1: Mechanism of action of Quetiapine fumarate.

5-HT_{1A}, 5HT_{2A} and 5HT_{2C} -Types of serotonin 5-hydroxytryptamine receptor, D₂- Dopamine receptor, H₁ - Histamine receptors, α_1 and α_2 -Types of adrenergic receptors, NRI- Noradrenaline Reuptake Inhibitor.

Due to high affinity for 5HT_{1A} receptors, norquetiapine increases serotonergic transfer of impulses by the raphe neurons in brain and fluctuate 5HT performance in the limbic and cortical regions and in the hippocampus, it stimulate neuron regeneration by increase in the release of brain-derived neurotrophic factor.

Adverse effects

Quetiapine and norquetiapine causes sedation, hypnosis, increased appetite and weight gain due to action on H₁ receptors. Quetiapine and norquetiapine causes blockage of α_1 which produces orthostatic hypotension. Norquetiapine due to strong antagonism at muscarinic (M₁, M₃, M₅) receptors causes dry mouth, urine accumulation, pupillary dilatation, increase in intraocular pressure, hypothermia, hyperglycemia and diabetes [23].

Dosage

Table 2 showed FDA-approved doses for quetiapine IR and quetiapine ER. Adjustments in doses can be made, depending on clinical response and tolerability of the patient [25,26,27].

Classical mood stabilizer has less efficacy and narrow therapeutic index in intense manic, mixed episodes of bipolar disorder. In contrast, QF was superior in management of intense manic and mixed episodes as monotherapy or adjunctive to classical mood stabilizers for bipolar depression with low side effect. Brand names

for QF are showed in table 3 [28].

Literature survey

Exhaustive literature survey was carried out using different research, published reports pertaining to QF through different databases like Google scholar, Science direct, Pub med central, Scopus etc. Information regarding QF was collected by using different keyword such as SNEDDS, SMEDDS, SLN, etc. on above mentioned databases. Most of the information was derived from various reports published between years 2011 to 2018.

Panzade P. et al. formulated directly compressible orodispersible tablets containing QF as drug. Orodispersible tablets were prepared by sublimation method. Full factorial design (32) was used to study the

effect of concentration of Indion 414 (superdisintegrant) and concentration of camphor (subliming agent). Different batches were formulated with varying concentration of Indion 414 (3-5% w/w) and camphor (5-15 % w/w). The evaluation test such as thickness, weight variation, content uniformity, porosity, disintegration time and in vitro drug release was carried. The formulation F3 was selected as optimized batch due to less disintegration time, greater drug release. The formulation with 5% w/w of each Indion 414 and camphor was optimized. The disintegration time was 18.66 seconds. Scanning electron microscopy (SEM) of tablet, before and after sublimation showed presence of pores on surface. Differential scanning calorimetric (DSC) showed no excipient incompatibility. Stability studies showed no remarkable changes in drug content and in vitro disintegration time. Thus Indion 414 and

Table 2: FDA-approved indications.

FDA approved indications	Quetiapine IR (Dose mg/day and year of approval)	Quetiapine ER (Dose mg/day and year of approval)
Schizophrenia		
Adults	150-750 BID /TID and 1997	400-800 and 2007
Adolescents (13-17 years)	400-800 BID	Not approved
Bipolar disorder		
Bipolar mania, adults	400-800 BID as monotherapy/ adjunct and 2003	400-800 once a day as monotherapy/ adjunct and 2008

Table 3: Available brand names for quetiapine fumarate.

Brand name	Dose of drug	Manufactured by
Qmax Tablet	25 mg and 100 mg	ACI Limited
Qpine Tablet	25 mg and 100 mg	Sanofi Bangladesh LTD
Quetimax Tablet	25 mg	Novartis (Bangladesh) Ltd.
Quetinil Tablet	25 mg and 100 mg	Albion Pharmaceuticals Ltd.
Quiet Tablet	25 mg and 100 mg	Incepta Pharmaceuticals Limited
Quiet Tablet (Extended Release)	50 mg	Incepta Pharmaceuticals Limited
Qutap Tablet	25 mg and 100 mg	Healthcare Pharmaceuticals Ltd.
Qutipin Tablet	25 mg and 100 mg	Sun Pharmaceutical (Bangladesh) Limited
Qutipin SR Tablet (Sustained Release)	50 mg, 200 mg and 300 mg	Sun Pharmaceutical (Bangladesh) Limited
Seroquet Tablet	25 mg and 100 mg	UnimedUnihealth MFG. Ltd.
Seroquet ER Tablet (Extended Release)	50 mg	UnimedUnihealth MFG. Ltd.
Sizofree Tablet	25 mg and 100 mg	Eskayef Bangladesh Ltd.
Tiapine Tablet	25 mg and 100 mg	General Pharmaceuticals Ltd.
Tiapine XR Tablet (Extended Release)	50 mg and 200 mg	General Pharmaceuticals Ltd.
Toliken Tablet	25 mg and 100 mg	Delta Pharma Limited

camphor have significant effect on dependant responses. Hence, using experimental design optimum formulation can be developed in shorter time. Sublimation would be an effective approach for the development of ODTs [29].

Porfire A et al. developed sustained release quetiapine tablets by applying quality by design approach. D-optimal design was used for formulation of various batches. The level and ratio of matrix forming agents and type of diluents were chosen as independent variable. The dependent variables were the cumulative % of drug release and time intervals. Optimized formulation showed zero order release and a dissolution profile same as to the standard product (Seroquel XR200 mg), with similarity factor values f_2 of 74.53 and 83.74. Thus sustained release tablets were developed successfully by using the quality by design approach [30].

Murthy RR et al. prepared solid lipid nanoparticles (SLN) containing QF and hemifumarate. Glyceryl monostearate (solid lipid), poloxamer 407 (surfactant) and soya lecithin (stabilizers) were used as excipient. SLNs were prepared by using a hot melt emulsification high-pressure homogenization method. SLNs were evaluated by particle size, polydispersity and entrapment efficiency. SLNs of quetiapine hemifumarate and QF with particle size of 101.1 nm and 93.6 nm and 101.1 nm were obtained respectively. In vitro drug release study showed Higuchi model as best fitted model for both QF and quetiapine hemifumarate SLNs. These studies showed a remarkable increase in quetiapine hemifumarate drug in brain in case of SLN as compared to the respective drug solutions [31].

Rao NGR et al. prepared QF fast disintegrating tablets by using direct compression method. Solvent evaporation method was used to prepare QF and eudragit E100 complex. The QF was reduced and masked after forming complex with eudragit EPO in distinct ratios. Taste evaluation was carried out on human volunteers. Crospovidone showed better drug release as compared with other superdisintegrants. The results concluded that drug's bitter taste was masked with enhanced dissolution [32].

Sevukarajan M et al. prepared QF hydrogel with chitosan, Sodium alginate and different ratios of Hydroxy propyl methyl cellulose HPMC to achieve controlled release formulation. The formulations were evaluated for SEM, swelling index, and entrapment efficiency (EF) and in-vitro dissolution. Drug EF and water uptake capacity of

hydrogel beads increased with increase in % and grade of HPMC (K100, K15 and K4). Drug release was reduced as the polymer concentration was increased. Formulation F4 has showed good in-vitro dissolution profile. Thus it conclude that controlled drug delivery systems were formulated successfully with polymeric network [33].

Talele SG et al. designed self nanoemulsifying drug delivery system (SNEDDS) for QF. SNEDDS was optimized by using test such as particle size, zeta potential and drug release by using response surface methodology. Labrafac lipophile WL, tween 80, capryol 90 was used as oil, surfactant, and cosurfactant respectively. Pseudoternary phase diagrams of oil, surfactant or co surfactant, and water were constructed. A optimized formulation with 0.57ml of tween 80, 0.19ml labrafac lipophile WL and 0.30ml of capryol 90 was prepared [34].

Vadlamudi HC et al. formulated quetiapine self microemulsifying drug delivery system formulation. Solubility of drug was taken in oils, surfactants and cosurfactants. Pseudoternary phase diagram was plotted. Optimized liquid self microemulsifying drug delivery systems (SMEDDS) were converted into solid SMEDDS by adsorption and melt granulation method. Batches were tested for micromeritic properties, drug release, stability and antipsychotic activity for amphetamine induced stereotypy and swimming normalization test. Solid self microemulsifying drug delivery system showed good micromeritics properties, 96% of drug release and drug content of 80 to 90%. Formulation O13 showed 1.2 years of shelf life and showed better antipsychotic activity [35].

Shah B et al. prepared QF microemulsion with and without chitosan. QF microemulsion and chitosan microemulsion was evaluated for globule size, pH and viscosity. Chitosan microemulsion with particle size of 35.31 ± 1.71 nm showed highest ex-vivo nasal diffusion ($78.26 \pm 3.29\%$) in 8 hours with no sign of damage of skin. By using intranasal route the result showed, 2.7 and 3.8 folds higher bioavailability with chitosan microemulsion compared to QF microemulsion and drug solution respectively [36].

Pokharkar V et al. formulated QF nanoemulsion for intranasal delivery. The different HLBs of Emalex LWIS 10, PEG 400 and transcutool P were used as co-surfactants, capmul MCM was used as oil, tween 80 was used as a surfactant and water as vehicle. Pseudoternary-phase diagrams were plotted. Prepared nanoemulsion was tested for globule size, in vitro dissolution, transmission

electron microscope and brain-targeting efficiency. Optimized nanoemulsion formulation showed globule size of 144 ± 0.5 nm and twofold increase in drug release as compared with drug. In vivo study was performed on rats. The intranasal administration of QF loaded nanoemulsion showed shorter T_{max} compared to intravenous administration [37].

Veerabrahma K et al. developed SLN using three different lipids such as glyceryl trimyristate, glyceryl tristearate and glyceryl monostearate. SLN were prepared by hot homogenization and then ultrasonication method. DSC was used to study drug excipient compatibility. Optimized formulation F3 showed particle size of 200-250 nm with varying entrapment efficiency in range between 80% - 92%. The physical stability was carried out at room temperature after two months. In vivo studies were performed in male wistar rats showed increase in relative bioavailability of QF by 3.71 times as compared with the reference drug suspension [38].

Elmenoufy GA et al. compared the efficacy of QF and QF-loaded SLN (QFSLN). Schizophrenia was induced to rats was by intraperitoneal ketamine injection for 1 week. To estimate the antipsychotic effect of QF, a low dose (LD) of 10 mg/kg and a high dose (HD) of 30 mg/kg were orally administrated to two groups of rats (designated L.QF and H.QF) for 3 weeks (2 weeks without ketamine injection; the last week with ketamine). Two other groups of rats were administered equivalent low and high doses of QF in its SLN form orally for 3 weeks, after 1 hour of ketamine injection. QFSLN treatment showed enhanced effect over QF in a dose dependent manner with minimal side effects in schizophrenic rats [39].

Upadhyay P et al. QF simple and liposomal dispersion were prepared in simulated nasal fluid pH 6.8, characterized and compared for diffusion through sheep nasal mucosa by ex vivo drug diffusion within 6 h. After 6 h liposomal dispersion showed 32.61 ± 1.70 and the simple dispersion showed 27.56 ± 1.33 for % drug diffusion. It was found that diffusion coefficient for liposomal dispersion was higher than simple dispersion. Liposomal dispersion showed Hopfenberg model and non-Fickian super case II anomalous transport and simple dispersion showed Higuchi model and Fickian diffusion mechanism. Results of in vivo, ciliotoxicity, and gamma scintigraphy studies on mice confirmed liposome appropriate for taking through nasal route for brain delivery [40].

Conclusions

This systematic review underlines the effectiveness of quetiapine monotherapy for bipolar I and II disorder and schizophrenia. Quetiapine fumarate may have a protective effect on mal treatment of mania. In nutshell this review gives idea about detail information about quetiapine fumarate along with literature survey of different dosage forms of quetiapine fumarate. Quetiapine fumarate is ideal candidate for development for novel drug delivery system such as nanostructured lipid carrier, more studies in these areas are required. The lower risk of headache in quetiapine treated patients with acute bipolar depression should require study. The evidence for the use of quetiapine combined with mood stabilizers in children and adolescents with acute bipolar depression is very small to support the clinical practice.

Declarations

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Authors' contributions

All authors contributed to the preparation of the manuscript.

References

1. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch Gen Psychiatry*. 2007; 64(5):543-552. DOI: <https://doi.org/10.1001/archpsyc.64.5.543>
2. Li P, Andreopoulos S, Warsh J. Signal transduction abnormalities in bipolar affective disorder. In: Reith MEA, editor. *Cerebral signal transduction*. Totowa: Humana Press; pp. 283-312. DOI: https://doi.org/10.1007/978-1-59259-019-3_11
3. Warsh J, Young L, Li P. Guanine nucleotide binding (G) protein disturbances. In: Manji H, Bowden C, Belmaker R, editors. *Bipolar medications: mechanisms of action*. Washington: *American Psychiatric Press*. pp. 299-329.
4. Young LT, Li PP, Kish SJ, et al. Cerebral cortex Gs alpha protein levels and forskolin-stimulated cyclic AMP formation are increased in bipolar affective disorder. *J Neurochem*. 1993; 61:890-898. PMID: <https://www.ncbi.nlm.nih.gov/pubmed/8395565>
5. Wang HY, Friedman E. Enhanced protein kinase C

- activity and translocation in bipolar affective disorder brains. *Biol Psychiatry*. 1996; 40:568-575. DOI: [https://doi.org/10.1016/0006-3223\(95\)00611-7](https://doi.org/10.1016/0006-3223(95)00611-7)
6. Manji HK, Quiroz JA, Payne JL, et al. The underlying neurobiology of bipolar disorder. *World Psychiatry*. 2003; 2(3): 136-146. DOI: https://doi.org/10.1007/7854_2014_290
7. Goodwin FK, Jamison KR. Manic-depressive illness. Oxford: Oxford University Press; 1990; pp.65. Available from: <https://vdocuments.mx/manic-depressive-illness-fk-goodwin-and-kr-jamison-oxford-university.html>
8. Smith K. The difference between bipolar disorder 1 and 2. *PSYCOM*. 1986; Available from: <https://www.psycom.net/bipolar-disorder-difference-one-two>
9. Suttajit S, Srisurapanont M, Maneeton N, Maneeton B. Quetiapine for acute bipolar depression: a systematic review and meta-analysis and meta-analysis. *Drug Design, Development and Therapy*. 2014; 8:827-838. DOI: <https://doi.org/10.2147/DDDT.S63779>
10. Lavretsky H. History of schizophrenia as a psychiatric disorder. In: Mueser KT, Jeste DV, editors. Clinical handbook of schizophrenia. New York: Guilford Press. 2008; pp.3-12. Available from: [http://old.ncpz.ru/siteconst/userfiles/file/englit/Kim%20T.%20Mueser%20PhD%20\(Editor\),%20Dilip%20V.%20Jeste%20MD%20\(Editor\)%20-%20Clinical%20Handbook%20of%20Schizophrenia.pdf](http://old.ncpz.ru/siteconst/userfiles/file/englit/Kim%20T.%20Mueser%20PhD%20(Editor),%20Dilip%20V.%20Jeste%20MD%20(Editor)%20-%20Clinical%20Handbook%20of%20Schizophrenia.pdf)
11. Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: a pathophysiologic approach. 9th ed. McGraw-Hill. 2014; pp.1019-1046. Available from: <https://accesspharmacy.mhmedical.com/book.aspx?bookid=689>
12. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *PT*. 2014; 39(9):638-645. PMID: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159061/>
13. Schizophrenia. Available from: <https://www.nimh.nih.gov/health/publications/schizophrenia/index.shtml>
14. Brown AS. The environment and susceptibility to schizophrenia. *Progress in neurobiology*. 2011; 93(1):25-58. DOI: <https://doi.org/10.1016/j.pneurobio.2010.09.003>
15. Beck AT, Rector NA, Stolar N, Grant P. Schizophrenia: cognitive theory, research, and therapy. New York: Guilford Press. 2009; pp.30-61. Available from: <https://psycnet.apa.org/record/2008-17980-000>
16. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*. 1999; 20(3):201-225. DOI: [https://doi.org/10.1016/S0893-133X\(98\)00060-8](https://doi.org/10.1016/S0893-133X(98)00060-8)
17. Diagnostic and statistical manual of mental disorders. 5th ed. American psychiatric association. 2013; pp.89-122. DOI: <https://doi.org/10.1176/appi.books.9780890425596>
18. Argo TR, Crimson ML, Miller AL, et al. Schizophrenia treatment algorithms Texas medication algorithm project procedural manual. Texas Department of State Health Services. 2008; DOI: <http://www.dshs.tx.us/mhprograms/TIMA.shtm>
19. Thase ME. Quetiapine monotherapy for bipolar depression. *Neuropsychiatr Dis Treat*. 2008; 4(1):21-31. PMID: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515925/>
20. Sanford M, Keating GM. Quetiapine: a review of its use in the management of bipolar depression. *CNS Drugs*. 2012; 26 (5):435-460. Available from: <https://www.readbyqxmd.com/read/22519923/>
21. Grunze H, Vieta E, Goodwin GM, et al. WFSBP Task force on treatment guidelines for bipolar disorders the world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: Update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry*. 2010; 11(2):81-109. DOI: <https://doi.org/10.3109/15622970903555881>
22. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013; 15(1):1-44. DOI: <https://doi.org/10.1111/bdi.12025>
23. Muneer A. Pharmacotherapy of bipolar disorder with quetiapine: A recent literature review and an update. *Clin PsychopharmacolNeurosci*. 2015; 13(1):25-35. DOI: <https://dx.doi.org/10.9758%2Fcpn.2015.13.1.25>
24. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *The American journal of psychiatry*. 2000; 157:514-20. DOI: <https://doi.org/10.1176/appi.ajp.157.4.514>
25. Astra Zeneca Pharmaceuticals LP. Seroquel

- (quetiapine fumarate) prescribing information. DOI: <http://www1.astrazeneca-us.com/pi/seroquel.pdf>
27. AstraZeneca Pharmaceuticals LP. Seroquel XR (quetiapine fumarate) prescribing information. DOI: <http://www1.astrazeneca-us.com/pi/seroquelxr.pdf>.
 28. Guzman F. Quetiapine indications: fda-approved and off-label uses. *Psychopharmacology Institute*. 2013; Available from: <https://psychopharmacologyinstitute.com/antipsychotics/quetiapine/quetiapine-indications/>
 29. Quetiapine fumarate. Available from: <https://medex.com.bd/generics/940/quetiapine-fumarate/brand-names>.
 30. Panzade P, Kalyankar P, Lahoti S. Formulation design and optimization of orodispersible tablets of quetiapine fumarate by sublimation method. *Indian Journal of Pharmaceutical Sciences*. 2015; 77(3):267-273. PMID: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4502140/>
 31. Porfire A, Gavan A, Marina C, Tomuta I. Formulation and pharmaceutical development of quetiapine fumarate sustained release matrix tablets using a QbD approach. *Acta Pharm*. 2017; 67:53-70. DOI: <https://doi.org/10.1515/acph-2017-0009>
 32. Murthy RR, Lohan S, Sharma S. Formulation and evaluation of solid lipid nanoparticles of quetiapine fumarate and quetiapine hemifumarate for brain delivery in rat model. *Pharmaceutical nanotechnology*. 2013; 1:239-247. Available from: <https://sci-hub.tw/10.2174/22117385113019990005>
 33. Rao NGR, Reddy MR, Krishna D. Formulation and design of taste masked quetiapine fumarate orally fast disintegrating tablets. *Asian Journal of Pharmaceutical and Clinical Research*. 2013; 6(2):70-75. Available from: <https://www.researchgate.net/publication/287397035>
 34. Sevukarajan M, Nair KJR, Jeyachitra B. Preparation and characterization of hydrogel Based Drug Delivery System of quetiapine fumarate. *International journal of chemical and pharmaceutical sciences*. 2011; 2(2):19-25. Available from: <http://www.ijcps.com/files/vol2issue2/3.pdf>
 35. Talele SG, Derle DV. Response surface methodology as a tool for optimization of self-nanoemulsified drug delivery system of quetiapine fumarate. *Asian Journal of Pharmaceutics*. 2017; 11(4):319-330. Available from: <https://www.asiapharmaceutics.info/index.php/ajp/article/view/1628>
 36. Vadlamudi HC, Yalavarthi PR, Nagaswaram T, Rasheed A, Peesa JP. In-vitro and pharmacodynamic characterization of solidified self microemulsified system of quetiapine fumarate. *J Pharm Investig*. 2018; (49):161-172 DOI: <https://doi.org/10.1007/s40005-018-0397-1>
 37. Shah B, Khunt D, Misra M, Padh H. Non-invasive intranasal delivery of quetiapine fumarate loaded microemulsion for brain targeting: Formulation, physicochemical and pharmacokinetic consideration. *European Journal of Pharmaceutical Sciences*. 2016; 91:196-207. DOI: <https://doi.org/10.1016/j.ejps.2016.05.008>
 38. Pokharkar V, Boche M. Quetiapine nanoemulsion for intranasal drug delivery: Evaluation of brain-targeting efficiency. *AAPS Pharm Sci Tech*. 2017; 18(3):686-696. DOI: <https://doi.org/10.1208/s12249-016-0552-9>
 39. Veerabrahma K, Narala A. Preparation, characterization and evaluation of quetiapine fumarate solid lipid nanoparticles to improve the oral bioavailability. *Journal of Pharmaceutics* 2013; 2013:1-7. DOI: <https://doi.org/10.1155/2013/265741>
 40. Elmenoufy GA, Said MM. Evaluation of quetiapine fumarate and its Solid Lipid Nanoparticles as antipsychotic drug in rat model of schizophrenia. *Biomedical Research and Therapy*. 2017; 4(8):1480-1497. DOI: <https://doi.org/10.15419/bmrat.v4i08.203>
 41. Upadhyay P, Trivedi J, Pundarikakshudu K, Sheth N. Comparative study between simple and optimized liposomal dispersion of quetiapine fumarate for diffusion through nasal route. *Drug Delivery*. 2016; 23(4):1214-1221. DOI: <https://doi.org/10.3109/10717544.2015.1120364>

Copyright: © **Patil et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.