PHARMACOGENETICS OVERVIEW OF QUETIAPINE FOR MENTAL HEALTH DISORDERS

Syifa Khairani[1], Shofura Marsa[1]*, Melisa I. Barliana[2,3], Neily Zakiyah[3,4]

[1]Undergraduate Study Program, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia
[2]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia
[3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia
[4]Center of Excellence in Higher Education for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia
shofura.marsa29@gmail.com
diserahkan 05/06/2024, diterima 01/07/2024

ABSTRACT

Severe mental health disorders, such as schizophrenia and bipolar, often require treatment with atypical antipsychotic drugs, yet many patients exhibit incomplete responsiveness and adverse effects. This has led to the exploration of pharmacogenetics to personalize treatment potentially. Quetiapine, a commonly used atypical antipsychotic, is often used in mental health disorders for depressive episodes. Its pharmacokinetics and pharmacodynamics are potentially influenced by genetic variations in Cytochrome P450 (CYP) enzymes, Dopamine receptor D3 (DRD3), and other genes. Previous studies investigated the impact of genetic variants on quetiapine metabolism, revealing possible associations with CYP2D6, CYP2C19, Catechol-O-methyltransferase (COMT), and other genes. Notably, the COMT variant rs13306278 was linked to increased quetiapine exposure. CYP3A5 and CYP2B6 phenotypes also affected quetiapine variability, with the ATP-binding cassette super-family G member 2 (ABCG2) variant rs2231142 associated with quetiapine accumulation. Recent pharmacogenetic advancements emphasize individualized treatment based on genetic profiles, particularly considering interactions with CYP3A4. Although concerns exist regarding drug-drug interactions and limited efficacy in certain conditions, integrating genetic information into clinical practice holds promise for optimizing quetiapine therapy and improving patient outcomes.
Keywords: CYP, pharmacogenetics, treatment, quetiapine.

INTRODUCTION

Quetiapine, classified as a second-generation antipsychotic (SGA) medication, is utilized for treating of various mental disorders, encompassing schizophrenia, depression, bipolar disorder, and generalized anxiety disorder in monotherapy (Lalonde & Van Lieshout, 2011). As an atypical antipsychotic approved by the US Food and Drug Administration (FDA) in 1997, Quetiapine possesses a distinct receptor-binding profile (Borison et al., 1996)

Derived from dibenzothiazepine, quetiapine is prescribed for individuals displaying symptoms of psychotic disorders and has demonstrated comparable efficacy to traditional antipsychotics when treating schizophrenia in the near term (Arvanitis & Miller, 1997; Peuskens & Link, 1997; Small et al., 1997). In the context of bipolar disorder, quetiapine is specifically prescribed to address moderate to severe manic episodes, major depressive episodes, and as a preventive measure against the return of manic or depressed episodes in people who have been diagnosed with type II bipolar disorder who have demonstrated a positive response to previous quetiapine treatment (Lalonde & Van Lieshout, 2011). Furthermore, quetiapine is used as monotherapy for treating of generalized anxiety disorder (GAD). While certain studies propose that second-generation antipsychotics (SGAs) are generally ineffective for GAD, quetiapine exhibits the potential to alleviate specific symptoms associated with the disorder. Moreover, it appears to offer benefits for patients using selective serotonin reuptake medications for obsessive-compulsive disorder (LaLonde & Van Lieshout, 2011; Poyurovsky & Weizman, 2021).

Rigorous randomized controlled clinical trials have proved the efficacy of quetiapine in addressing schizophrenia symptoms while exhibiting a low likelihood of inducing extrapyramidal signs. Quetiapine is available in various strengths, ranging from 25 to 300mg. It has shown efficacy across a wide dosage range, with some studies examining doses as high as 750 mg/day (DeVane & Nemeroff, 2001). Quetiapine is available in tablet form, as well as in solution or suspension, with varying dosages tailored to patient characteristics, such as demographics and the severity of the specific disease being treated (Tran et al., 2021)

When administered orally, quetiapine undergoes rapid absorption and extensive metabolism, first-pass metabolism results in an oral bioavailability of 9% (Lalonde & Van Lieshout, 2011). While the presence of food does not affect the absorption of the drug (DeVane & Nemeroff, 2001), it demonstrates linear pharmacokinetics within the recommended dosage range (100 to 375 mg twice a day or 75 to 250 mg three times daily). Approximately 83% of plasma proteins bind quetiapine (DeVane & Nemeroff, 2001). Metabolism of the drug primarily occurs the liver excretes less than 5% of the initial medication in cytochrome P450 (CYP) system, with the majority detected in urine (approximately 73%) and feces (21%) (Zubiaur et al., 2021).

Drug metabolism is the chemical modification of drug molecules once they reach the body. Generally, this process reduces the therapeutic effects of drugs. During drug biotransformation, most drugs convert their lipophilic centers to hydrophilic centers, increasing their water solubility and facilitating elimination through urine or bile. This is an important stage in drug metabolism because medicines lipophilic characteristic allows them to remain in the body for longer periods of time, potentially causing toxicity.

CYP enzymes, which rely on heme,

oxidize steroids, fatty acids, and xenobiotics in mammals. They are necessary for medication metabolism, hormonal control, and drug interactions. Understanding CYP pathways is critical for healthcare professionals since different medications can inhibit, induce, or be substrates for specific CYP pathways, influencing drug levels and efficacy. Quetiapine is primarily metabolized by CYP3A4 and CYP2D6, and it undergoes considerable hepatic metabolism, with a significant percentage eliminated in urine and feces (Ayano, 2016)

Quetiapine exhibits a plasma protein binding rate of approximately 83%. It undergoes extensive metabolism less than 5% of the initial medication is eliminated in the liver via the CYP system (Friedman et al., 1997). Eighty-nine percent of the quetiapine dosage is metabolized by CYP3A4, with CYP2D6 mostly handling the remaining eleven percent, as well as additional enzymes such as CYP2C9, CYP2C19, and CYP3A5 (DeVane & Nemeroff, 2001).

Quetiapine generates eleven known metabolites, some of which possess activity while others are inactive. These metabolites can be classified into three classes according to their reactions: hydroxylated or sulfoxylate metabolites, dealkylated metabolites, and a mixture of both processes. The enzyme CYP3A4 metabolizes quetiapine into N-desalkyl quetiapine (which lacks quetiapine), and subsequently, CYP2D6 further processes it into 7-hydroxy N-alkylated quetiapine. Moreover, CYP2D6 directly converts quetiapine into 7-hydroxy quetiapine. All of these metabolites possess activity. The half-life of quetiapine (t1/2) is approximately 7 hours, and its maximum concentration (Cmax) is achieved 1-2 hours after oral administration (tmax). Additionally, quetiapine inhibits CYP2C9, CYP3A4, CYP2D6, CYP2C19, and CYP1A2. Recent studies indicate that the enzyme catechol O-methyltransferase (COMT) is involved in the intermediate metabolic processes of quetiapine (Ortega-Ruiz et al., 2022).

This review aims to examine the role of pharmacogenetics in tailoring quetiapine treatment for concerned mental diseases including bipolar disorder and schizophrenia. It highlights the influence of genetic variations, particularly in Cytochrome P450 enzymes and other genes, on quetiapine's pharmacokinetics and pharmacodynamics. Additionally, it investigates how these genetic differences might impact drug metabolism and effectiveness, emphasizing the potential of utilizing genetic profiles to optimize quetiapine therapy and enhance patient outcomes, despite existing concerns about drug interactions and limited effectiveness in certain situations.

This review underscores the urgency of optimizing quetiapine treatment for mental disorders by examining genetic variations. The review highlights how these differences influence quetiapine's pharmacokinetics and pharmacodynamics. Understanding these genetic factors can enhance therapeutic efficacy, minimize adverse effects, and address current limitations in treatment, such as drug interactions and variable effectiveness. Ultimately, the review advocates for incorporating genetic profiles into clinical practice to personalize quetiapine therapy, improve patient outcomes, and guide future research and policy development in psychiatric pharmacotherapy.

METHODS

A literature search was performed in PubMed using keywords such as "quetiapine," "pharmacogenetics," "CYP," and "treatment." The search focused on articles published between 2013 and 2023, resulting in around 90 articles. This review's inclusion criteria were papers detailing

Figure 1. Article Selection Method

quetiapine medication, studies investigating pharmacogenetics, particularly the interaction between quetiapine and CYP enzymes, and research presenting clinical outcomes or impacts on patients as a result of these interactions.

After a thorough examination, for full-text review, 25 articles that met the inclusion criteria were selected. Twelve of these studies were included to be reviewed narratively. Two reviewers extracted data independently, concentrating on research features, patient demographics, CYP enzyme interactions, and clinical results.

RESULTS AND DISCUSSIONS

Antipsychotic drugs like quetiapine are frequently used in the treatment of schizophrenia and bipolar disorder and are a crucial component of long-term therapy (Riedel et al., 2007). Due to its capacity to lessen both negative and positive symptoms, such as apathy and social disengagement, quetiapine is one of the most often used atypical antipsychotics for schizophrenia (Riedel et al., 2007) Positive symptoms include delusions and hallucinations. Typically, quetiapine is used at modest doses initially, with dosage increases made gradually in accordance with patient response and drug tolerance (Valentine et al., 2024)

To ensure successful therapy, it is imperative to conduct routine monitoring of treatment efficacy and adverse effects, such as weight gain, drowsiness, and risk of metabolic diseases (Valentine et al., 2024) Long-term results can also be enhanced by psychosocial interventions such cognitive-behavioral therapy, social support, and education for patients and their families (Hardoy et al., 2005).

Quetiapine is used as maintenance therapy in both manic and depressive periods, as well as to treat the acute phase of bipolar illness (Suppes et al., 2009). Quetiapine dosages are modified based on the patient's response and the stage of the bipolar cycle (Riedel et al., 2007). It's also necessary to regularly evaluate side effects

including weight gain and sleep problems, as well as how the body responds to the medication and for the best long-term treatment outcomes, combination therapy with psychosocial programs or mood stabilizers is frequently advised (Hardoy et al., 2005).

3.1. Quetiapine for mental health disorders

Schizophrenia, a debilitating neurological and psychiatric disorder, frequently calls for the usage of atypical antipsychotic medications, which are also used to treat bipolar disorder (Correll & Scholer, 2020; Kahn et al., 2015). Despite their widespread use, a considerable number of patients exhibit incomplete responsiveness to these medications and may suffer from adverse effects, including weight gain and metabolic disturbances (Tandon et al., 2010; Leucht et al., 2013). Consequently, developing a genetic test to determine the most suitable antipsychotic treatment early in the illness is of significant clinical value. Such a test would enable personalized treatment strategies, potentially improving patient outcomes.

Given that schizophrenia affects approximately 1% of the global population, it is crucial to maintain social functioning and prevent symptom relapse through continuous, long-term treatment (Kahn et al., 2015; Leucht et al., 2013). However, individual responses to antipsychotic medications vary significantly, underscoring the need to identify additional markers associated with drug response (Muñoz-Berbel & Panov Panov, 2022).

Quetiapine, an atypical antipsychotic, is also extensively used to treat depressive episodes in bipolar disorder. While it can enhance treatment adherence, quetiapine is associated with several adverse drug reactions (ADRs). The most notable ADRs includes dizziness (15-27%), somnolence (25-39%), headache (10-23%), metabolic effects such as weight gain (11-30%), and hypotension (6-18%) (Zubiaur et al., 2021). These ADRs are generally dose-dependent, except for the metabolic effects, which need continuous exposure to the drug and are dose-independent (Kanba et al., 2019; Poyurovsky & Weizman, 2021).

The potential of pharmacogenetics in tailoring antipsychotic treatment for mental health disorders is becoming increasingly evident. Healthcare providers can tailor treatments to individual patients by identifying genetic markers influencing drug response, enhancing treatment efficacy, and minimizing adverse effects. This strategy shows potential for improving the management of schizophrenia and related disorders, paving the way for more effective and personalized medical care.

3.2. Pharmacogenetics of quetiapine

Quetiapine's active metabolite is responsible for its antidepressant qualities, which make it a popular medication for the treatment of bipolar disorder and schizophrenia (Cabaleiro et al., 2015). The presence of CYP3A4 inhibitors can elevate quetiapine levels, while gender and genetic variations in DRD3 and CYP1A2 genes influence its pharmacokinetics. Variations in the CYP2C19 gene impact its pharmacodynamics, while genetic differences in CYP1A1 and CYP2C9 can affect somnolence (Cabaleiro et al., 2015). Notably, a study isolated quetiapine's effects in healthy participants, confirming that its antidepressant properties primarily stem from N-desalkylquetiapine (Cabaleiro et al., 2015).

CYP3A4, a clinically relevant biomarker, significantly influences the metabolism of various drugs, including quetiapine (Beunk et al., 2023). Genetic variants, such as C3435T, impact drug elimination differently across medications, yet

a study on healthy subjects found no significant alterations regarding quetiapine, indicating the role of other genetic factors, P-glycoprotein, produced in the ATP-binding cassette, subfamily B member 1 (ABCB1) gene, at the central nervous system drug disposition (Saiz-Rodríguez et al., 2018). In vitro assays investigating quetiapine's interaction with P-glycoprotein have produced conflicting results, suggesting the need for further research (Beunk et al., 2023).

Recent research has made significant strides in understanding the pharmacogenomics of schizophrenia treatment, identifying associations between treatment response and various genes, including CYP2D6, CYP2C19, Catechol-O-methyltransferase (COMT), ATP-binding cassette super-family B member 1 (ABCB1), Dopamine Receptor D3 (DRD3), and 5-Hydroxytryptamine Receptor 2C (HTR2C (Muñoz-Berbel & Panov Panov, 2022). New potential candidates such as TRAF2 and NCK-interacting protein kinase (TNIK), Reelin (RELN), Neurogenic locus notch homolog 4 (NOTCH4), and Solute Carrier Family 6 Member 2 (SLC6A2) have emerged, along with specific gene combinations like the haplotype rs1544325-rs5993883-rs6269-rs4818 in COMT, linked to treatment response across multiple antipsychotic drugs (Muñoz-Berbel & Panov Panov, 2022). Through multivariate interactions analysis, a predictive factor surfaced: the combination of rs6269 in COMT and rs3813929 in HTR2C, showing potential for enhancing clinical response to antipsychotics (Muñoz-Berbel & Panov Panov, 2022). Genotyping efforts among schizophrenia inpatients revealed intriguing associations, notably the link between the SNP rs4986893 in CYP2C19 and the response to quetiapine treatment (Muñoz-Berbel & Panov Panov, 2022).

Although there is strong evidence advocating for personalized medicine based on pharmacogenetic research, there are no existing guidelines recommending quetiapine dosage adjustments based on genetic polymorphisms. A recent study explored the influence of genetic variants in pharmacogenes on the pharmacokinetics of quetiapine and the occurrence of adverse drug reactions in 49 healthy participants (Zubiaur et al., 2021). The genotyping of 80 variants across 19 pharmacogenes uncovered significant associations, such as the COMT rs13306278 T allele, which correlated with increased quetiapine exposure (Zubiaur et al., 2021). The study also identified metabolites like 7,8-dihydroxy-quetiapine and 7,8-dihydroxy-N-desalkyl-quetiapine, likely products of COMT, which may influence quetiapine accumulation via negative feedback mechanisms involving CYP2D6 and CYP3A4 (Zubiaur et al., 2021). Furthermore, variations in CYP3A5 and CYP2B6 phenotypes were shown to affect quetiapine exposure, highlighting their role in its metabolism (Zubiaur et al., 2021). The ABCG2 rs2231142 T allele was linked to quetiapine accumulation, indicating its significance in the drug's disposition (Zubiaur et al., 2021). Additional research is needed to validate the clinical relevance of these findings.

3.3. Recent advancements in the pharmacogenetics of quetiapine

The Dutch Pharmacogenetics Working Group (DPWG) has developed evidence-based guidelines that highlight pharmacogenetic interactions involving specific genes and antipsychotic medications, including quetiapine. These guidelines recommend considering dose adjustments based on individual genotypes, particularly for interactions involving quetiapine and CYP3A4 (Beunk et al., 2023; Cabaleiro et al., 2015).

Quetiapine is primarily metabolized by CYP3A4, with potential interactions from CYP3A4 inhibitors like ketoconazole increasing quetiapine levels, and inducers like phenytoin or carbamazepine decreasing them. Genetic variability in CYP2D6, CYP3A5, and ABCB1 has been studied to influence quetiapine metabolism and serum concentrations (Ortega-Ruiz et al., 2022). Notably, Bakken et al. (2015) discovered that the CYP2D6 phenotype strongly impacted the The serum levels of N-desalkylquetiapine, but not quetiapine itself, while genetic variability in ABCB1 and CYP3A5 did not affect quetiapine or its metabolite (Bakken et al., 2015).

In contrast, CYP3A4 plays a crucial role in quetiapine metabolism, influenced by genetic factors that affect its pharmacokinetics (Beunk et al., 2023). However, further research is needed to understand the clinical implications of these genetic variations fully. Gender differences also affect quetiapine and N-desalkylquetiapine blood levels, with males generally exhibiting higher concentrations due to increased CYP3A4 expression. Therapeutic drug monitoring (TDM) can guide treatment but has limitations that must be considered (Beunk et al., 2023).

The DPWG and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been instrumental in providing pharmacogenetic guidelines for antipsychotics, emphasizing the interaction between quetiapine and CYP2D6. Existing guidelines underscore the role of CYP3A4 in personalizing quetiapine pharmacotherapy, highlighting the importance of individual genetic factors in treatment decisions (Rudå et al., 2021).

Concerns about potential drug-drug interactions (DDIs) with quetiapine mostly involve the CYP3A4 metabolic pathway, this may raise the risk of quetiapine interval prolongation. This is particularly relevant in managing behavioral and psychological symptoms of dementia (BPSD), where current guidelines advise against quetiapine use due to limited efficacy and significant risks. Alternatives such as pimavanserin show promise, but further research is needed to evaluate their therapeutic role and assess potential interactions (Van Der Weide & Van Der Weide, 2014).

Recent pharmacogenetic advancements provide valuable insights into quetiapine metabolism, drug interactions, and personalized treatment approaches. Integrating genetic information into clinical practice can potentially improve treatment outcomes and minimize adverse effects, underscoring the need for ongoing research and guideline development in this field.

The application of pharmacogenomics applications in medicine in the world and in Indonesia has increased the efficiency and safety of treatment, and improved the quality of life of patients. Globally, pharmacogenomics is used to improve the efficiency and safety of schizophrenia treatment. For example, one study found that genes associated with response to antipsychotic drugs can help predict treatment effectiveness and reduce the risk of side effects. In Indonesia, pharmacogenomics applications are also applied in various supportive therapies to reduce suicidal urges in schizophrenia patients. Research found that supportive therapy with guidance techniques can help reduce suicidal ideation and improve patients' quality of life (Pardede, 2017).

In addition, acquaintance therapy is used in Indonesia to address social isolation in patients with schizophrenia, with results showing an increase in social interaction skills and a decrease in symptoms of social isolation. Social therapy is also used to improve social interaction skills, with studies showing improved verbal and non-verbal skills and reduced symptoms of social

isolation. Supportive therapy has also been used to improve emotion management in patients with schizophrenia, with studies showing improved coping skills and reduced intrapsychic conflict (Pombaile & Hidayati, 2023).

In the application of pharmacogenomics applications, Indonesia has developed several initiatives, such as the development of a pharmacogenomics information system and the use of information technology to improve treatment efficiency and safety. However, more research and development is still needed to improve the quality of life of patients and reduce the medical burden in Indonesia. With the continued development of research and technology, as well as increased awareness and education, it is expected that pharmacogenomics will become a standard in global and national clinical practice (Mutiara, 2017).

CONCLUSION

Quetiapine, a second-generation antipsychotic licensed by the FDA in 1997, efficiently treats a variety of mental health conditions, including bipolar disorder, depression, and generalized anxiety disorder. Its unique receptor-binding profile and extensive hepatic metabolism, primarily mediated by CYP3A4 and CYP2D6, contribute to its efficacy and safety. Clinical trials have highlighted its effectiveness in managing schizophrenia with minimal risk of extrapyramidal symptoms. Pharmacogenetic research has furthered our understanding of quetiapine's metabolism and drug interactions, emphasizing the importance of CYP3A4 in dose adjustments based on individual genotypes. Integrating pharmacogenetic information into clinical practice can enhance treatment outcomes and minimize adverse effects. However, challenges remain in managing drug-drug interactions involving quetiapine and its metabolizing enzymes. Overall, pharmacogenetic advancements are paving the way for personalized medicine in quetiapine therapy, necessitating further research and guideline development to optimize its clinical utility and improve patient outcomes.

FUTURE DIRECTION

Future research should focus on validating genetic markers that influence quetiapine metabolism and response in diverse patient populations. Prospective studies are needed to establish robust guidelines for pharmacogenetic testing and application in clinical settings. Additionally, further exploration of alternative treatments and potential drug combinations will contribute to more effective management strategies for mental health disorders.

REFERENCES

Arvanitis, L. A., & Miller, B. G. (1997). Multiple fixed doses of "seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. *Biological Psychiatry*, *42*(4), 233–246. https://doi.org/10.1016/S0006-3223(97)00190-X

Ayano, G. (2016). Psychotropic Medications Metabolized by Cytochromes P450 (CYP) 2D6 Enzyme and Relevant Drug Interactions. Clinical *Pharmacology & Biopharmaceutics 2016 5:4*, *5*(4), 1–4. https://doi.org/10.4172/2167-065X.1000162

Bakken, G. V., Molden, E., & Hermann, M. (2015). Impact of genetic variability in CYP2D6, CYP3A5, and ABCB1 on serum concentrations of quetiapine and N-desalkylquetiapine in psychiatric

patients. *Therapeutic Drug Monitoring*, *37*(2), 256–261. https://doi.org/10.1097/FTD.0000000000000135

Basile, V. S., Masellis, M., Potkin, S. G., & Kennedy, J. L. (2002). Pharmacogenomics in schizophrenia: the quest for individualized therapy. *Human molecular genetics*, *11*(20), 2517–2530. https://doi.org/10.1093/hmg/11.20.251

Beunk, L., Nijenhuis, M., Soree, B., de Boer-Veger, N. J., Buunk, A. M., Guchelaar, H. J., Houwink, E. J. F., Risselada, A., Rongen, G. A. P. J. M., van Schaik, R. H. N., Swen, J. J., Touw, D., van Westrhenen, R., Deneer, V. H. M., & van der Weide, J. (2023). Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. *European Journal of Human Genetics 2023 32:3*, *32*(3), 278–285. https://doi.org/10.1038/s41431-023-01347-3

Borison, R. L., Arvanitis, L. A., & Miller, B. G. (1996). ICI 204,636, an atypical antipsychotic: Efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *Journal of Clinical Psychopharmacology*, *16*(2), 158-169.

Cabaleiro, T., López-Rodríguez, R., Román, M., Ochoa, D., Novalbos, J., Borobia, A., Carcas, A., & Abad-Santos, F. (2015). Pharmacogenetics of quetiapine in healthy volunteers: association with pharmacokinetics, pharmacodynamics, and adverse effects. *International Clinical Psychopharmacology*, *30*(2), 82–88. https://doi.org/10.1097/YIC.0000000000000047

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric Disease and Treatment*, 16, 519-534. https://doi.org/10.2147/NDT.S225643

DeVane, C. L., & Nemeroff, C. B. (2001). Clinical pharmacokinetics of quetiapine: An atypical antipsychotic. *Clinical Pharmacokinetics*, *40*(7), 509–522. https://doi.org/10.2165/00003088-200140070-00003/METRICS

Friedman, J. H., Bishnoi, I. R., Perel, J. M., & Henkel, J. (1997). Quetiapine: A new atypical antipsychotic drug. *Journal of Clinical Psychopharmacology*, *17*(3), 190-197.

Gajwani, P., Muzina, D. J., Kemp, D. E., Gao, K., & Calabrese, J. R. (2007). Update on quetiapine in the treatment of bipolar disorder: results from the BOLDER studies. *Neuropsychiatric disease and treatment*, *3*(6), 847–853. https://doi.org/10.2147/ndt.s1636

Hardoy, M. C., Garofalo, A., Carpiniello, B., Calabrese, J. R., & Carta, M. G. (2005). Combination quetiapine therapy in the long-term treatment of patients with bipolar I disorder. *Clinical Practice and Epidemiology in Mental Health : CP & EMH*, *1*(7), 7. https://doi.org/10.1186/1745-0179-1-7

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., ... & Insel, T. R. (2015). Schizophrenia. *Nature Reviews Disease Primers*, *1*(1), 1-23. https://doi.org/10.1038/nrdp.2015.67

Kanba, S., Murasaki, M., Koyama, T., & et al. (2019). Long-term mood/antidepressant effects of quetiapine extended-release formulation: An open-label, non-controlled

extension study in Japanese patients with bipolar depression. *BMC Psychiatry*, 19, 198. https://doi.org/10.1186/s12888-019-2181-9

LaLonde, C. D., & Van Lieshout, R. J. (2011). Treating generalized anxiety disorder with second generation antipsychotics: A systematic review and meta-analysis. *Journal of Clinical Psychopharmacology*, *31*(3), 326–333. https://doi.org/10.1097/JCP.0B013E31821B2B3F

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., ... & Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*, *382*(9896), 951-962. https://doi.org/10.1016/S0140-6736(13)60733-3

Muñoz-Berbel, X., & Panov Panov, G. (2022). Early Markers in Resistant Schizophrenia: Effect of the First Antipsychotic Drug. *Diagnostics 2022*, Vol. *12*, Page 803, 12(4), 803. https://doi.org/10.3390/DIAGNOSTICS12040803

Hardoy, M. C., Garofalo, A., Carpiniello, B., Calabrese, J. R., & Carta, M. G. (2005). Combination quetiapine therapy in the long-term treatment of patients with bipolar I disorder. *Clinical Practice and Epidemiology in Mental Health : CP & EMH*, *1*(7), 7. https://doi.org/10.1186/1745-0179-1-7

Mutiara, M. (2017). Penerapan Terapi Suportif untuk Meningkatkan Manajemen Emosi Negatif pada Individu yang Memiliki Pasangan Skizofrenia. *Jurnal Muara Ilmu Sosial, Humaniora, Dan Seni*, *1*(1), 105. https://doi.org/10.24912/jmishumsen.v1i1.340

Pardede, S. (2017). Penerapan terapi suportif dengan teknik bimbingan untuk mengurangi dorongan bunuh diri pada pasien skizofrenia. *TERAPUTIK: Jurnal Bimbingan Dan Konseling*, *1*(1), 89. https://doi.org/10.26539/117

Pombaile, N. P. Z., & Hidayati, L. N. (2023). Penerapan Terapi Berkenalan Dalam Mengatasi Gejala Isolasi Sosial Pada Pasien Skizofrenia: Studi Kasus. *JKJ): Persatuan Perawat Nasional Indonesia*, *11*(2), 333–345.

Riedel, M., Müller, N., Stradding, M., Spellmann, I., Severus, E., & Möller, H. J. (2007). Quetiapine in the treatment of schizophrenia and related disorders. *Neuropsychiatric Disease and Treatment*, *3*(2), 219. https://doi.org/10.2147/NEDT.2007.3.2.219

Suppes, T., Vieta, E., Liu, S., Brecher, M., & Paulsson, B. (2009). Maintenance treatment for patients with bipolar I disorder: Results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *American Journal of Psychiatry*, *166*(4), 476–488. https://doi.org/10.1176/APPI.AJP.2008.08020189/ASSET/IMAGES/LARGE/U316T4.JPEG

Valentine, M. J., Kayastha, A., Newsome-Cuby, T. R., Nguyen, A. T. N., Fisher, R. G., Pham, H. M., Meimon, S. A., Phu, A., Parry, C. A., Nelson, J. J., Hayes, E. C., & Muranjan, S. (2024). A Clinical Suspicion of Quetiapine-Induced Psychosis: A Case Report and Literature Review. *Cureus*, *16*(1). https://doi.org/10.7759/CUREUS.52167

Ortega-Ruiz, M., Soria-Chacartegui, P., Villapalos-García, G., Abad-Santos, F., & Zubiaur, P. (2022). The Pharmacogenetics of Treatment with Quetiapine. *Future Pharmacology 2022*, Vol. *2*, Pages 276-286,

2(3), 276–286. https://doi.org/10.3390/FUTUREPHARMACOL2030018

Pardede, S. (2017). Penerapan terapi suportif dengan teknik bimbingan untuk mengurangi dorongan bunuh diri pada pasien skizofrenia. *TERAPUTIK: Jurnal Bimbingan Dan Konseling*, *1*(1), 89. https://doi.org/10.26539/117

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta psychiatrica Scandinavica*, *96*(4), 265–273. https://doi.org/10.1111/j.1600-0447.1997.tb10162.x

Pombaile, N. P. Z., & Hidayati, L. N. (2023). Penerapan Terapi Berkenalan Dalam Mengatasi Gejala Isolasi Sosial Pada Pasien Skizofrenia: Studi Kasus. *JKJ): Persatuan Perawat Nasional Indonesia*, *11*(2), 333–345.

Potkin, S. G., Preskorn, S., Hochfeld, M., & Meng, X. (2013). A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. *Journal of Clinical Psychopharmacology*, *33*(1), 3–10. https://doi.org/10.1097/JCP.0B013E31827C0314

Poyurovsky, M., & Weizman, A. (2021). Quetiapine for bipolar depressive episode in obsessive-compulsive disorder patients maintained on selective serotonin reuptake inhibitor treatment. *Clinical Neuropharmacology*, *44*(4), 123–125. https://doi.org/10.1097/WNF.0000000000000456

Riedel, M., Müller, N., Stradding, M., Spellmann, I., Severus, E., & Möller, H. J. (2007). Quetiapine in the treatment of schizophrenia and related disorders. *Neuropsychiatric Disease and Treatment*, *3*(2), 219. https://doi.org/10.2147/NEDT.2007.3.2.219

Rudå, D., Jensen, K. G., Decara, M. S., Klauber, D. G., Fagerlund, B., Møllegaard, J. R., Linnet, K., Werge, T., Correll, C. U., Fink-Jensen, A., Jürgens, G., & Pagsberg, A. K. (2021). CYP2D6 Genotyping and Antipsychotic-Associated Extrapyramidal Adverse Effects in a Randomized Trial of Aripiprazole Versus Quetiapine Extended Release in Children and Adolescents, Aged 12-17 Years, With First Episode Psychosis. *Journal of Clinical Psychopharmacology*, *41*(6), 667–672. https://doi.org/10.1097/JCP.0000000000001490

Saiz-Rodríguez, M., Belmonte, C., Román, M., Ochoa, D., Jiang-Zheng, C., Koller, D., Mejía, G., Zubiaur, P., Wojnicz, A., & Abad-Santos, F. (2018). Effect of ABCB1 C3435T Polymorphism on Pharmacokinetics of Antipsychotics and Antidepressants. *Basic & Clinical Pharmacology & Toxicology*, *123*(4), 474–485. https://doi.org/10.1111/BCPT.13031

Small, J. G., Hirsch, S. R., Arvanitis, L. A., Miller, B. G., & Link, C. G. (1997). Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. *Archives of general psychiatry*, *54*(6), 549–557. https://doi.org/10.1001/archpsyc.1997.01830180067009

Suppes, T., Vieta, E., Liu, S., Brecher, M., & Paulsson, B. (2009). Maintenance treatment for patients with bipolar I disorder: Results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). *American Journal of Psychiatry*, *166*(4), 476–488. https://doi.org/10.1176/APPI.AJP.2008.08020189/ASSET/IMAGES/LARGE/U316T4.JPEG

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2010). Schizophrenia, "just the facts" 5. Treatment and prevention. Past, present, and future. *Schizophrenia Research*, *122*(1-3), 1-23. https://doi.org/10.1016/j.schres.2010.05.025

Tran, J., Gervase, M. A., Evans, J., Deville, R., & Dong, X. (2021). The stability of quetiapine oral suspension compounded from commercially available tablets. *PLOS ONE*, *16*(8), e0255963. https://doi.org/10.1371/JOURNAL.PONE.0255963

Valentine, M. J., Kayastha, A., Newsome-Cuby, T. R., Nguyen, A. T. N., Fisher, R. G., Pham, H. M., Meimon, S. A., Phu, A., Parry, C. A., Nelson, J. J., Hayes, E. C., & Muranjan, S. (2024). A Clinical Suspicion of Quetiapine-Induced Psychosis: A Case Report and Literature Review. *Cureus*, *16*(1). https://doi.org/10.7759/CUREUS.52167

Van Der Weide, K., & Van Der Weide, J. (2014). The influence of the CYP3A4*22 polymorphism on serum concentration of quetiapine in psychiatric patients. *Journal of Clinical Psychopharmacology*, *34*(2), 256–260. https://doi.org/10.1097/JCP.0000000000000070

Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., Huai, C., Shen, L., Zhang, N., He, L., & Qin, S. (2021). Cytochrome P450 Enzymes and Drug Metabolism in Humans. *International Journal of Molecular Sciences*, *22*(23). https://doi.org/10.3390/IJMS222312808

Zubiaur, P., Fernández-Campos, P., Navares-Gómez, M., Soria-Chacartegui, P., Villapalos-García, G., Román, M., Mejía-Abril, G., Ochoa, D., & Abad-Santos, F. (2021). Variants in comt, cyp3a5, cyp2b6, and abcg2 alterquetiapine pharmacokinetics. *Pharmaceutics*, *13*(10), 1573. https://doi.org/10.3390/PHARMACEUTICS13101573/S1