Rapid Titration of Clozapine: Clinical Insights, Benefits, Risks, and Applications

Author: Riley Bowen, PharmD
Mentor: Hannah Norris, PharmD, BCPS

Program Number: 2024-09-03
Approved Dates: 12/1/2024 – 6/1/2025
Approved Contract Hours: One Hour(s) (1.0) CE(s)

Learning Objectives:

1. Understand the pharmacological basis and process of rapid clozapine titration
2. Evaluate the clinical advantages and disadvantages of rapid clozapine titration
3. Apply best practices for rapid clozapine titration in clinical settings

Background

Clozapine, developed in 1956 by Hunziker, Schmutz, and Stille at the Wander Laboratories in Berne, Switzerland, was engineered with the specific goal of revolutionizing neuroleptic and antipsychotic treatment. Designed to minimize motor side effects and mitigate the risk of neuroleptic malignant syndrome (NMS), clozapine has consistently demonstrated superiority over both typical (first-generation) and atypical (second-generation) antipsychotics in treating treatment-resistant schizophrenia and schizoaffective disorder.[1,2] It has earned its place as the gold standard pharmacotherapeutic intervention for these challenging conditions by the 2020 American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Schizophrenia. Additionally, clozapine has been shown to be effective in the treatment of refractory bipolar affective disorder (BPAD) with and without psychotic features.[3,4] Use of clozapine has well established advantages, including superiority for positive symptoms (delusions, hallucinations, and disorganized speech) in treatment-resistant patients, higher quality of life and longer time to discontinuation, improvement in cognition contributing to better work and social functioning, and significantly less extrapyramidal side effects (EPS).[1,5] It also has reduced suicidality, risk of relapse, psychiatric admissions, and psychotropic comedications compared to other treatments and can even reduce tardive dyskinesia (TD) severity.[1,5]

The purpose of this article is to educate pharmacists on rapid titration of clozapine by discussing the advantages, disadvantages, side effects, and clinical applications of this potentially life-changing therapy.

Pharmacological Basis of Clozapine

Clozapine functions as an antagonist at both dopamine type 2 (D_2) and serotonin type 2_A ($5\text{-}HT_{2A}$) receptors. Notably, clozapine exhibits weak and loosely bound affinity to D_2 receptors, resulting in occupancy levels below 60%, which is thought to contribute to its minimal risk of EPS. Conversely, clozapine demonstrates a heightened affinity for D_4 receptors. Furthermore, clozapine exerts antagonistic effects on various other receptors, including alpha-adrenergic, histamine H_1, cholinergic, and additional dopaminergic and serotonergic receptors.[6]

In addition to its recognized antipsychotic effects, clozapine is acknowledged for its potential mood-stabilizing benefits attributed to its demonstrated reduction in suicidality and efficacy in patients with BPAD

lacking psychotic features.[3,4] While relatively infrequent, patients grappling with treatment-refractory schizophrenia, schizoaffective disorder, or BPAD may manifest severe agitation and aggression. Substantial data supports the utilization of clozapine as a maintenance treatment for individuals displaying persistent aggressive behavior, a recommendation endorsed in the 2020 APA Practice Guideline for the Treatment of Patients With Schizophrenia.[2] Importantly, it is hypothesized that the anti-aggressive effects of clozapine may operate independently from its antipsychotic properties.[7]

Clozapine is administered orally and is well-absorbed from the gastrointestinal tract. Peak plasma concentrations are typically reached within 2.5 hours after ingestion. Metabolism occurs primarily in the liver through cytochrome (CYP) P450 enzymes, mainly CYP1A2, with contributions from CYP2D6, CYP2C19, and CYP3A4. Major metabolites include norclozapine and clozapine N-oxide, both of which are pharmacologically active. The metabolism can be influenced by factors, such as smoking which induces CYP1A2 and co-administration of other medications. There is substantial variation between individuals in clozapine plasma levels. Plasma levels on a specific dosage will generally be greater in nonsmokers, heavy caffeine users, women, and in older individuals.[3] The significant heterogeneity in plasma levels is thought to be explained in part by the large number of genes contributing to its metabolism.[8] Therapeutic drug monitoring is not always performed, though if levels are collected, clozapine's therapeutic effect is typically observed at plasma levels of 350-600 ng/mL (clozapine only, no metabolites).

Traditional vs. Rapid Titration

Clozapine is most often initiated in the inpatient setting under close supervision and monitoring. Despite the proven superior efficacy of clozapine, it remains underutilized in inpatient settings. One contributing factor is the traditional slow titration period, which can be a hindrance within budget and resource-limited institutions.[9,10,11] The APA schizophrenia practice guideline and manufacturer recommendations recommend starting with 12.5 to 25 mg per day, increasing the daily dose, as tolerated, in increments of 25 to 50 mg at intervals ≥1 day to a target dose of 300 to 450 mg/day in 1 to 3 divided doses by the end of 2 weeks. It may be further titrated in increments not exceeding 100 mg and no more frequently than once or twice weekly to a maximum total daily dose of 900 mg. From this point on, this 2-week-long regimen will be described as the traditional or slow titration method. The traditional titration method was not established through controlled trials but was instead based on reports of severe hypotension during initial clinical testing of clozapine on inmates in the United States in 1974 and case series linking high dosages to the occurrence of seizures.[12,13] The traditional approach in certain cases is thought to be a conservative approach and not applicable to all patients.[14] Slow titration of clozapine delays the onset of controlling psychotic symptoms, often requiring supplementary pharmacotherapy, such as benzodiazepines, to supplement the treatment. This can result in prolonged suffering and an extended length of stay for patients.[8,23]

The definition of “rapid” titration varies slightly between institutions, but the most common regimen is as follows: a dose of 25 mg, followed by 25 to 50 mg administered as needed every 6 hours in the first 24 hours (maximum of 100 mg day 1). On subsequent days, the dose is increased by not more than 100 mg each day until satisfactory symptom control (i.e., absence of behavior dangerous to self or others and remission or substantial reduction of positive symptoms).[4,8] The initial 25 mg dose acts as a test dose of clozapine to decide about subsequent slow or rapid clozapine titration. As mentioned above, the typical time to peak plasma levels of clozapine is 2.5 hours, so a 6-hour interval should provide ample time to assess risk and severity of any acute side effects. Rapid titration of clozapine may be appropriate for patients where the urgent resolution of symptoms is more critical than avoiding adverse side effects.[23] This strategy can be necessary in cases of aggression, severe self-neglect, or extreme distress.[23] Rapid titration should only take place within the inpatient setting with close monitoring and can be used in both clozapine-naive patients and those with a clozapine history.

Advantages of Rapid Titration

In 2014, Ifteni and colleagues published a retrospective chart review evaluating the effectiveness and safety of rapid clozapine titration in 111 patients with schizophrenia. Symptom control was obtained with an average dose of 353 ± 174 mg/day after 4.1 ± 3.1 days in the 73 patients previously treated with clozapine. For the 38 patients initially started on other antipsychotics, the average clozapine dose required for symptom control was 409 ± 188 mg/day and was reached after 7.1 ± 4.8 days. In this study, concomitant benzodiazepines and mood stabilizers were avoided for safety reasons, and satisfactory symptom control was achieved after 5 days. No serious adverse events were observed, including severe hypotension,

agranulocytosis, syncope, and seizures. This study showed rapid clozapine titration can be used safely and effectively while providing more rapid symptom control and reducing polypharmacy.[8]

In a retrospective cohort study conducted by Poyraz et al, among individuals with treatment-refractory schizophrenia, there was a notable trend towards a shorter interval from clozapine initiation to discharge in the rapid titration group compared to the conventional titration group (22.4 ± 8.72 vs. 27.0 ± 10.5 days, p=0.1). Additionally, a significant reduction in the total duration of hospitalization was observed in the rapid titration cohort (29.6 ± 10.6 vs. 41.2 ± 14.8 days, p=0.002). It is noteworthy that hypotension emerged as a more prevalent adverse event in the rapid titration arm, with one patient exhibiting symptoms suggestive of myocarditis. Overall, the rapid titration approach demonstrated favorable safety and efficacy outcomes. While the post-initiation length of stay trended lower in the rapid titration group, this difference did not reach statistical significance. Nevertheless, the combined strategy of early clozapine initiation alongside rapid titration significantly shortened the duration of hospitalization.[3]

A recent retrospective study, by Ifteni et al. assessed the rapid titration of clozapine in treatment-refractory BPAD (n=44). In the rapid titration group, the mean maximum dose of clozapine was 361 mg/day, reached after 4.2 days, compared to a mean maximum dose of 387 mg/day in the standard titration group, which was reached after 12.4 days. The proportion of patients requiring benzodiazepines after clozapine initiation was smaller in the rapid titration group (87.0% vs 63.6%, p=0.044). The overall length of stay was 26.3 ± 10.8 days in the rapid titration group and 33.3 ± 10.4 days in the standard titration group (p=0.013). The number of days from starting clozapine until readiness for discharge was significantly shorter in the rapid titration group after adjusting for the proportion of patients with psychotic features and the number of inpatient antipsychotic trials and psychotropic comedications (12.7 ± 6.3 vs. 16.5 ± 5.8; p=0.0077).[4] No major adverse drug reactions were observed. The number of patients suffering a relapse during the 12 months after discharge was similar in the two groups (54.6% vs. 47.8%, p=0.60).[4] The difference of 3.8 days between the two titration schedules was both statistically significant and clinically significant. It is important to note that, at this particular institution, the standard titration schedule used was faster than the generally utilized and recommended dosing schedule, so if compared to the traditional guideline recommendation, the size of effect would likely be even larger.[2] All of this to say, a shortened hospital stay could result in significant budget and resource savings within an institution while still providing similar safety and efficacy results in patients with treatment-refractory BPAD.[4] These results support the findings by Ifteni and colleagues that also showed that rapid clozapine titration was effective and safe in patients with schizophrenia.[8]

In a case series reported by Aksoy Poyraz et al., four patients underwent an "ultra-rapid" clozapine titration for treatment-resistant mania with psychotic features after receiving written consent from the patients' families.[14] The first patient, a 20-year-old with a complex psychiatric history, showed persistent agitation and hyperactivity despite multiple medications. A modified rapid titration approach was used, starting with 50 mg in the morning and 100 mg in the evening on Day 1 and reaching 350 mg by Day 5. The patient's mania improved rapidly within the first few days of clozapine treatment, and by Day 26, they were discharged in stable condition on clozapine, aripiprazole, and valproic acid.[14]

Patient 2, aged 23, received a similar clozapine regimen with additional haloperidol on Day 1. It was reported they had significant recovery in their mental state on the first-day clozapine was introduced. This led to significant improvement by Day 18. Patient 3, aged 19, showed similar progress and was discharged with a stable mood after 28 days. The final patient, aged 31, experienced reduced agitation with rapid clozapine titration and was discharged on Day 65. No serious adverse effects were observed during rapid titration of clozapine except sedation, which occurred in two patients and was reportedly desired at the beginning of their hospitalization.[14] All four of these patient cases received even higher initial doses of clozapine than the usual rapid titration regimen and still managed to support the previous findings by Ifteni and colleagues and by Poyraz et al. showing that rapid clozapine titration is effective and safe in patients with schizophrenia and BPAD.[3,4,8]

These findings support the advantages of rapid titration of clozapine over slow titration. Notably, rapid titration facilitates symptom control as early as day one, in contrast to the several days to weeks required with the traditional slow method. This accelerated approach not only achieves similar maximum and maintenance doses, but also significantly enhances patient outcomes. Furthermore, the expedited symptom relief contributes to shorter hospital stays, which is beneficial for both patients and healthcare providers. Additionally, rapid symptom control can reduce instances of workplace violence, improving safety for

healthcare staff. The resulting reduction in hospitalization duration yields substantial economic and logistical benefits for medical institutions. Importantly, these benefits are achieved without introducing significant side effects in this patient population.

Risks of Rapid Titration

The main concern with the rapid titration regimen is the potential for increased risk of adverse effects. Most commonly noted is the concern for orthostatic hypotension and seizures. Each of these are considered treatable and are themselves not considered grounds for termination of therapy. Both hypotension and seizures have been observed in patients using the most prudent dosing strategies available. In reference to these concerns, one recent case study and three retrospective chart reviews consisting of a total of 184 patients resulted in at most slightly more side effects and no serious adverse events.[3,4,8,14]

A 2012 case-control study from Australia by Ronaldson and colleagues concluded that rapid titration of clozapine was associated with an increased risk of myocarditis and reported that concomitant treatment with valproate increased the risk 2.6-fold.[15] Over a 16-year period (1993-2009), 105 patients met the predefined case definition for myocarditis, which included histological evidence or a combination of clinical cardiac dysfunction and diagnostic indicators (e.g., troponin levels ≥ 2x the upper limit of normal, echocardiogram, MRI) with onset occurring within 45 days of clozapine initiation. However, these findings have not been confirmed and are in disagreement with the evidence indicating that valproate can be used safely in conjunction with clozapine, both as augmentation in schizophrenia and for clozapine-induced seizures.[4]

In 2016, Lochhead and colleagues published a case report of a 21-year-old patient with schizophrenia who was initiated on rapid titration of clozapine. Approximately 10 days after initiating therapy, the patient demonstrated significant improvement in psychotic symptoms but rapidly developed rigidity, lethargy, and disorientation. The patient exhibited a fever of up to 106°F, a pulse rate of 120 beats per minute, and a CK level of 2733 U/L, leading to a diagnosis of NMS. The patient was provided supportive care and recovered to be discharged from the hospital. Per the report of the author, it remains unclear whether the NMS was due to the rapid titration or secondary to treatment with multiple antipsychotics, interactions between medications, initiation of clozapine in general, or a combination of these.[5] Clozapine has less risk of NMS as compared to first-generation antipsychotics. Recent studies have shown clozapine-induced NMS to have an atypical presentation with a slightly longer duration but overall lower clinical severity.[16]

The limited current data and various other confounding factors make it difficult to assess the true incidence and risk of orthostatic hypotension, seizures, myocarditis, and NMS in patients undergoing rapid titration of clozapine therapy. Below is a table of some of the acute risks that can occur with clozapine in general during traditional dosing as well as incidence, dependence on dose, and management of such an event.

Table 1: Acute Risks Associated with Traditional Clozapine Dosing: Incidence, Dose Dependence, and Management Strategies

Adverse Effect (AE)[17]	Incidence[17,18,16,19,20]	Dose Dependent[17,18]	Management[17,18,19]
Neutropenia	3%	No	ANC 1000-1499/μL; continue treatment with thrice weekly ANC monitoring until > 1500/μL[19] ANC 500-999/μL; interrupt treatment, hematology-oncology consult recommended, resume treatment once ANC ≥ 1000 /μL[19] May use lithium in case of rechallenge[17]
Agranulocytosis	0.7%	No	ANC < 500/μL; stop treatment, hematology-oncology consult recommended, rechallenge not recommended[19]

Orthostatic Hypotension	9%	First-dose effect*	Generally considered a manageable AE; treated with fludrocortisone or midodrine
Sedation	44%, often mild and transient, occurring in initial phase of treatment	Yes	Generally considered a manageable AE; avoid other sedating medications if able; dose or titration adjustment
Myocarditis	0.015-0.188%; more common in the first months of treatment	No	Troponin levels 2 times the upper limit of normal, or ST-segment elevation; discontinue; rechallenge not recommended
Cardiomyopathy	0.02–0.1%	No	Echocardiography-confirmed diagnosis; discontinue; rechallenge not recommended
Constipation or Obstruction/ Ileus	25%; 0.8%, respectively	Yes	Modify diet, exercise, utilize prophylactic laxative; if ileus/obstruction occurs, pause clozapine, and reintroduce after resolution of problem; stimulant laxative can be used short-term
Seizures	Doses > 600 mg/day ~ 4.4%; 300-600 mg/day ~2.7%; < 300 mg/day ~1.0%; more common in the initiation phase	Yes	Not grounds for termination, if seizure occurs; reduce dose by 50% or divide into multiple daily doses, look for other causes for lower seizure threshold, or treat with valproate or other antiepileptic drug without risk for bone marrow suppression
NMS	0.001-0.01%	No	Pause clozapine, check hydration, and consider intensive care unit referral until symptoms have fully resolved; electrolyte therapy if needed
The incidences of adverse effects listed above are not based upon data from rapid titration studies as the data is still too limited.			
**Clozapine is an α_1-adrenergic antagonist associated with a 'first-dose effect'. Patients are more likely to experience greater hypotensive effects when starting treatment or during dose increases. Desensitization of the α1-adrenergic receptors occurs with repeat exposure and tolerance often develops. There is considerable interpatient variability in both sensitivity to α_1-antagonists and metabolism of clozapine by cytochrome P450 enzymes.*[18]			

Clinical Application of Rapid Titration

As previously noted, rapid titration of clozapine may be appropriate for patients in whom rapid symptom resolution is prioritized over the potential risk of adverse side effects. This approach may be necessary in cases of aggression, severe self-neglect, or acute distress. Rapid titration should be conducted exclusively within inpatient settings for patients diagnosed with schizophrenia, schizoaffective disorder, or BPAD. It is important to acknowledge that patients eligible for rapid titration often lack the capacity to provide informed consent. In the studies referenced in this article, consent for treatment was obtained in accordance with the guidelines set forth by the respective hospital's ethics committee and/or through the patient's family member.

The following patient groups should generally avoid rapid titration of clozapine unless the treatment team has explicitly evaluated the associated risks and benefits: individuals under 18 years of age, patients with a history of epilepsy or clozapine-induced seizures, those with cardiovascular disease, patients with a history of clozapine-induced hypotension, individuals on antihypertensive medications, those with constipation or significant bowel disorders, patients with preexisting central nervous system conditions,[21] and older

patients, particularly those on medications that may cause orthostatic hypotension or who have poor hydration status.

During rapid titration, cessation of other antipsychotic medications is recommended to mitigate the cumulative impact of side effects. Pharmacists and healthcare providers should meticulously evaluate sedative and other mood-stabilizing medications administered during titration to evaluate appropriate continuation.

As per the 2020 APA schizophrenia practice guideline, substantial and rapid increments in clozapine dosage have been associated with instances of cardiovascular collapse and fatalities, particularly observed in patients concurrently prescribed respiratory depressant medications such as benzodiazepines.[2] It is important to acknowledge that this risk extends beyond the use of clozapine. Similarly, caution is advised against the simultaneous administration of intramuscular olanzapine and parenteral benzodiazepines due to the potential for heightened sedation and cardiorespiratory depression.[2]

Schulte and colleagues reported three cases of patients unable to tolerate the traditional slow clozapine titration protocol. One patient collapsed after the initial dose but continued with a reduced dose the next day. Another developed severe orthostatic hypotension, prompting a dose adjustment. The third patient experienced dizziness and sedation, which improved after reducing the dose. All patients showed significant improvement with gradual titration up to 200 mg daily. Consideration of concurrent medications is crucial during clozapine initiation. All three patients received scheduled lorazepam at doses between 1 mg daily to 2.5 mg three times daily, alongside the initiation of clozapine, and one of those patients was also prescribed a second antipsychotic,[22] both of which are capable of inducing sedation and cardiorespiratory depression. While it is not uncommon for severely agitated or distressed patients to receive multiple sedating medications, it is crucial to exercise caution and awareness. Administering these medications separately, with a minimum interval of 2 hours between administrations, can help mitigate the risk of oversedation and cardiorespiratory depression. This precaution is particularly important when complete avoidance of concomitant administration is not feasible.

Monitoring

The United States Food and Drug Administration and manufacturers of clozapine mandate adherence to the U.S. Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. This program serves as a robust safety monitoring framework crafted to mitigate the risks associated with neutropenia and agranulocytosis. It functions as a unified patient registry encompassing all products of clozapine manufacturers and facilitating the continuous tracking of absolute neutrophil counts (ANCs) and the systematic documentation of treatment decisions. The Clozapine REMS site offers detailed guidance on threshold values for ANCs, catering to both the general population and those with benign ethnic neutropenia, predominantly observed in individuals of African descent and characterized by ANCs lower than standard reference ranges.[19]

Below is a list of essential monitoring parameters to be observed when implementing a rapid clozapine titration approach.

Table 2: Essential Monitoring Parameters for Rapid Clozapine Titration

Monitoring Parameter[17,24]	Frequency of Monitoring[17,24]
Bowel Function	Daily while inpatient
CBC (ANC)	Baseline; weekly while inpatient
ECG	Baseline; repeat if significant change in dose or addition of other QTc-prolonging drugs
Echocardiogram	Baseline only if there are cardiac risk factors; repeat if signs or symptoms of myocarditis develop
Extrapyramidal Symptoms	Daily while inpatient; 4 weeks after initiation and dose change
Fall Risk	Daily while inpatient

Mental Status and Alertness	Daily while inpatient
Myocarditis Monitoring (C-reactive protein, eosinophils, troponin)	Weekly during first 6 weeks of treatment or if signs or symptoms of myocarditis develop
Serum Clozapine Concentration	As clinically appropriate
Smoking Patterns	Assess with initiation of clozapine and formulate plan for dose adjustment upon discharge if necessary
Vital Signs (Blood pressure, orthostatics, temperature, pulse, respiratory rate, oxygen saturation, AVPU scale [alert, verbal, pain, unresponsive], signs of infection)	Baseline; hourly on day 1, then twice daily while inpatient; at least weekly during first 3 to 4 weeks of treatment
Clozapine Dose	Dosing should be reviewed daily at minimum. If adverse effects present, dose may be reduced or not increased based on the review
New or Current Concomitant Medications Capable of Sedation or Cardiopulmonary Depression	Daily while inpatient

Conclusion

The rapid titration of clozapine has the potential to address urgent clinical needs in specific patient populations, particularly those requiring rapid symptom resolution due to aggression, severe self-neglect, or distress. Although rapid titration may be associated with higher risks of orthostatic hypotension, seizures, myocarditis, and NMS, current literature remains inconclusive regarding these risks. Nevertheless, rapid titration represents a valuable tool for individualizing clozapine treatment, similar to the use of ultra-slow titration for personalized care.

Rapid titration should be confined to inpatient settings for patients with schizophrenia, schizoaffective disorder, or BPAD. Follow facility-specific processes and protocols to obtain proper consent.

Certain patient groups should generally avoid rapid titration unless the treatment team has explicitly considered the risks and benefits. These groups include individuals under 18 years of age, those with a history of epilepsy or clozapine-induced seizures, patients with cardiovascular disease or previous clozapine-induced hypotension, those with constipation or significant bowel disorders, those on antihypertensive medications, individuals with preexisting central nervous system conditions, and older patients, particularly those on medications that may cause orthostatic hypotension or who have poor hydration status.

In summary, rapid clozapine titration offers a valuable strategy for certain patient subgroups requiring immediate symptom management, and it necessitates careful consideration of individual patient factors and close monitoring to ensure safety and efficacy.

References

1. Meltzer HY. Clozapine: Balancing Safety with Superior Antipsychotic Efficacy. Clinical Schizophrenia & Related Psychoses. 2012;6(3):134-144. doi:10.3371/CSRP.6.3.5
2. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. Third edition. American Psychiatric Association; 2021.
3. Poyraz CA, Özdemir A, Sağlam NGU, et al. Rapid Clozapine Titration in Patients with Treatment Refractory Schizophrenia. Psychiatr Q. 2016;87(2):315-322. doi:10.1007/s11126-015-9394-y
4. Ifteni P, Correll CU, Nielsen J, Burtea V, Kane JM, Manu P. Rapid clozapine titration in treatment-refractory bipolar disorder. Journal of Affective Disorders. 2014;166:168-172. doi:10.1016/j.jad.2014.04.020
5. Lochhead JD, Nelson MA, Schneider AL. Risks and benefits of rapid clozapine titration. Mental Illness. 2016;8(1). doi:10.4081/mi.2016.6457
6. Gammon D, Cheng C, Volkovinskaia A, Baker GB, Dursun SM. Clozapine: Why Is It So Uniquely Effective in the Treatment of a Range of Neuropsychiatric Disorders? Biomolecules. 2021;11(7):1030. doi:10.3390/biom11071030

7. Faden J, Citrome L. A systematic review of clozapine for aggression and violence in patients with schizophrenia or schizoaffective disorder. Schizophrenia Research. Published online 2024. doi:https://doi.org/10.1016/j.schres.2023.11.008
8. Ifteni P, Nielsen J, Burtea V, Correll CU, Kane JM, Manu P. Effectiveness and safety of rapid clozapine titration in schizophrenia. Acta Psychiatr Scand. 2014;130(1):25-29. doi:10.1111/acps.12241
9. Bryant-Comstock L, Stender M, Devercelli G. Health care utilization and costs among privately insured patients with bipolar I disorder. Bipolar disorders. 2002;4 6:398-405.
10. Dusetzina SB, Farley JF, Weinberger M, Gaynes BN, Sleath BL, Hansen RA. Treatment use and costs among privately insured youths with diagnoses of bipolar disorder. Psychiatric services. 2012;63 10:1019-1025.
11. Ekman M, Granström O, Omérov S, Jacob J, Landén M. The societal cost of bipolar disorder in Sweden. Soc Psychiatry Psychiatr Epidemiol. 2013;48(10):1601-1610. doi:10.1007/s00127-013-0724-9
12. Ramachandraiah CT, Subramaniam N, Tancer M. The story of antipsychotics: Past and present. Indian J Psychiatry. 2009;51(4):324-326. doi:10.4103/0019-5545.58304
13. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. Neurology. 1991;41(3):369-371. doi:10.1212/wnl.41.3.369
14. Aksoy Poyraz C, Turan Ş, Demirel ÖF, Usta Sağlam NG, Yıldız N, Duran A. Effectiveness of ultra-rapid dose titration of clozapine for treatment-resistant bipolar mania: case series. Therapeutic Advances in Psychopharmacology. 2015;5(4):237-242. doi:10.1177/2045125315584871
15. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: A case–control study. Schizophrenia Research. 2012;141(2):173-178. doi:https://doi.org/10.1016/j.schres.2012.08.018
16. Belvederi Murri M, Guaglianone A, Bugliani M, et al. Second-Generation Antipsychotics and Neuroleptic Malignant Syndrome: Systematic Review and Case Report Analysis. Drugs R D. 2015;15(1):45-62. doi:10.1007/s40268-014-0078-0
17. Nielsen J, Correll CU, Manu P, Kane JM. Termination of Clozapine Treatment Due to Medical Reasons: When Is It Warranted and How Can It Be Avoided? J Clin Psychiatry. 2013;74(06):603-613. doi:10.4088/JCP.12r08064
18. Tanzer TD, Brouard T, Pra SD, et al. Treatment strategies for clozapine-induced hypotension: a systematic review. Ther Adv Psychopharmacol. 2022;12:20451253221092931. Published 2022 May 24. doi:10.1177/20451253221092931
19. What is the clozapine Rems? Clozapine REMS. December 13, 2023. Accessed June 1, 2024. https://www.newclozapinerems.com/home.
20. Shirazi A, Stubbs B, Gomez L, et al. Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. Int J Mol Sci. 2016;17(6):863. Published 2016 Jun 2. doi:10.3390/ijms17060863
21. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients [published correction appears in Am J Psychiatry 1991 Oct;148(10):1427]. Am J Psychiatry. 1991;148(2):231-235. doi:10.1176/ajp.148.2.231
22. Schulte PFJ, Van Dijk D, Cohen D, Bogers J, Bakker B. Comment on 'effectiveness and safety of rapid clozapine titration in schizophrenia.' Acta Psychiatr Scand. 2014;130(1):69-70. doi:10.1111/acps.12274
23. Aksoy Poyraz C, Turan Ş, Demirel ÖF, Usta Sağlam NG, Yıldız N, Duran A. Effectiveness of ultra-rapid dose titration of clozapine for treatment-resistant bipolar mania: case series. Therapeutic Advances in Psychopharmacology. 2015;5(4):237-242. doi:10.1177/2045125315584871
24. Langford A, Hogan R. Protocol for rapid clozapine titration – for inpatients only. March 2022. Accessed June 1, 2024. http://www.oxfordhealthformulary.nhs.uk/docs/Rapid clozapine titration_ final.pdf.