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Review Article

Hematological Side Effects of Psychiatric Drugs

Running Title: Hematology and Psychiatric Drugs

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Abstract

This review article focuses on hematological disorders caused by psychiatric drugs, including neutropenia, leukopenia, leukocytosis, and anemia. Most major psychiatric drugs induce neutropenia and thrombocytopenia through various mechanisms, such as toxic bone marrow suppression and drug-dependent antineutrophil antibodies against hematopoietic precursors. Among these, agranulocytosis associated with phenothiazines is a well-discussed hematological side effect. Although rare, agranulocytosis is a dangerous and often fatal complication that may go unnoticed until infection occurs. We conducted a comprehensive literature search from 1977 to 2021, identifying 64 relevant articles. Our study aims to analyze outcomes related to pancytopenia, leucopenia, neutropenia, agranulocytosis, thrombocytopenia, and other hematological complications leading to hospitalization.

Keywords: Hematologic Diseases, Psychology, Adverse Effects, Complications, Medicine

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Introduction

Hematological adverse effects are possible with many psychiatric medications. These include anemia, leukocytosis, leukopenia, and neutropenia (1). Neutropenia and thrombocytopenia are common adverse effects associated with nearly all psychiatric drugs (1). Various pathomechanisms, such as peripheral neutrophil destruction, toxic bone marrow suppression, and drug-dependent anti-neutrophil antibodies, contribute to neutropenia (2). Phenothiazine-induced agranulocytosis, with an annual frequency of 3–12 cases per million, is a significant hematological side effect (1, 3). Thrombocytopenia, often of unclear etiology, may result from platelet dilution, clumping, splenic sequestration, or enhanced lysis (4). Despite its rarity, agranulocytosis is a serious and potentially fatal condition (5). Early recognition is crucial, as agranulocytosis often presents initially as flu-like symptoms (6, 7). However, few studies have investigated hematologic adverse drug reactions leading to hospitalization (8).

The purpose of this study is to analyze the outcomes of hematological side effects of psychiatric drugs, including pancytopenia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and other related conditions.

Methods

Literature Search

We conducted an extensive electronic search using databases such as Google Scholar, PUBMED, Embase, MEDLINE, Science Direct, PsycINFO, and ProQuest. The search covered articles published from 1977 to 2021. The following search terms guided our strategy: “hematological complication,” “hematologic complications,” “agranulocytosis,” “neutropenia,” “leukopenia,” “leukocytosis,” “thrombocytopenia,” “leukopenia,” “anemia,” “pancytopenia,” “hematological adverse impact,” and “immune thrombocytopenic purpura.” We excluded articles written in languages other than English and focused on case-control studies, case reports, randomized control trials, reviews, case series, animal studies, and toxicological studies.

Study Selection

From the search results, we identified 64 relevant articles. After reviewing titles and abstracts, we excluded 31 articles due to their repetitive nature or being case reports. The remaining 33 articles were included in our analysis.

Tricyclic Antidepressants (TCA):

Amitriptyline

Moustafa et al. investigated the hematological side effects of amitriptyline. They found a significant decrease in red blood cells, hemoglobin, packed cell volume, leukocytes, neutrophils, and lymphocytes. Patients using this drug should be aware of the potential occurrence of hematological complications and blood dyscrasia (9).

Imipramine

Aksoy et al. reported a case of thrombocytopenia caused by imipramine in a 5-year-old child (9).

Anderson et al. discussed acrocyanosis as a complication related to imipramine use in an 11-year-old girl (10).

ClomipramineMagni et al. presented a case report of a 54-year-old man who developed pancytopenia due to clomipramine treatment **.**Rack et al. observed hemoglobinuria as a transient complication of clomipramine infusion in one out of sixty patients (11).

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Selective Serotonin Reuptake Inhibitors (SSRIs)

Escitalopram

Bedel et al. reported a thrombocytopenia case occurring after escitalopram use in a 19-year-old female patient with generalized anxiety disorder (1).

Yadav et al. described uterine bleeding in a post-menopausal woman after starting escitalopram (2).

Fluoxetine

Pai et al. documented bruising associated with fluoxetine use in a 31-year-old patient with normal prothrombin time (3).

Myrsal H et al. reported ecchymosis in a 32-year-old female following 10 weeks of fluoxetine treatment; her hematological records remained within the normal range (3).

Paroxetine

Trewet et al. described a case of leukopenia induced by paroxetine in a 44-year-old white female (12).

Sertraline

Akcay et al. reported a rare occurrence of neutropenia after starting sertraline in a 16-year-old teenage boy. Only five cases of this complication were previously reported in the literature (13).

Asan et al. mentioned intermenstrual vaginal bleeding in a psychiatric patient taking sertraline (14).

Controlled Substance: Sibutramine

Ha et al. published a case report study in which a 24-year-old female developed sibutramine-induced necrotizing vasculitis (15).

Conventional Antipsychotics

Chlorpromazine

Canoso et al. discussed the anticoagulant effect of chlorpromazine. They found that partial thromboplastin time (PTT) and prothrombin time (PT) were prolonged in all four patients and one patient, respectively (16).

Kazama et al. reported thrombocytopenia associated with chlorpromazine use. Severe and persistent thrombocytopenia may occur due to an unknown mechanism of action, possibly affecting platelet production by megakaryocytes (17).

Haloperidol

A study in 2004 indicated iron deficiency anemia caused by chronic use of haloperidol (17).

In a case report, pancytopenia was discussed in an 85-year-old woman receiving haloperidol decanoate 50 mg IM monthly (18).

Another article reported decreased mean platelet volume (MPV) and red blood cell distribution width (RDW) in thirty patients with schizophrenia taking haloperidol (19).

Atypical Antipsychotics

Clozapine

Grover et al. conducted a study on psychotic patients treated with clozapine. Approximately one-tenth of the patients experienced hematological complications, including thrombocytopenia, anemia, eosinophilia, and neutropenia (3).

Two studies—one published in Italy in the Journal of Haematologica and the second in 1998—focused on neutropenia and agranulocytosis in patients treated with clozapine (20, 21).

Saman et al. reported that out of 3000 patients, 17 developed agranulocytosis. Among them, eight had fatal agranulocytosis, two had thrombocytopenia, and one was diagnosed with leukemia (22).

Davis et al. studied patients with treatment-resistant schizophrenia taking clozapine. Side effects, especially hematological ones, were a common reason for discontinuation (23).

Hummer et al. discussed clozapine-related hematological complications, including progressive neutropenia and transient disorders such as eosinophilia and leukocytosis (24).

Nielsen et al. emphasized regular hematological monitoring for clozapine. Regulations vary worldwide, but harmonization is recommended (25).

Lurasidone

Alageel et al. conducted a systematic review to explore the hematological safety of olanzapine. They searched electronic databases between 1998 and 2015 and identified 35 cases of olanzapine-induced leukopenia. Most of these cases occurred within the first month of olanzapine administration. Interestingly, more than two-thirds of the affected patients had not experienced drug-related leukopenia before taking olanzapine (27).

Sahoo et al. published a case report in the Indian Journal of Psychiatry. The report described an elderly schizophrenic patient who developed thrombocytopenia and leukopenia after starting olanzapine. This case highlights the susceptibility of elderly individuals to olanzapine's hematologic side effects, emphasizing the need for patient monitoring (28).

Cordes et al. reported three cases of reversible neutropenia during olanzapine therapy. In each case, the neutrophil count quickly returned to normal after olanzapine withdrawal (29).

Stergiou et al.

Stergiou et al. discussed a patient who developed leucopenia and neutropenia during treatment with olanzapine (28).

Quetiapine

Psychiatrica et al. assessed the effectiveness and safety of quetiapine in patients with uninterrupted bipolar disorder. Quetiapine was associated with two cases of temporary thrombocytopenia (30).

Romdhane et al., in the journal L'Encephale, reported a young male with initial schizophrenia who developed thrombocytopenic purpura following the use of quetiapine in combination with valproic acid (31).

Fan et al. discussed a case of a patient with bipolar disorder who experienced leukopenia and thrombocytopenia after taking quetiapine 400 mg/day and valproic acid 1000 mg/day for three and a half months. They concluded that quetiapine-associated leukopenia and thrombocytopenia might be reversible but potentially fatal (32).

Arslan et al. presented an uncommon case of leukopenia and thrombocytopenia after quetiapine 600 mg/day monotherapy in an elderly patient with bipolar disorder. Previous studies searched via the PubMed database showed 21 reported cases of leukopenia and neutropenia (33).

Cowan et al. documented a case of a female Caucasian patient who previously developed neutropenia and leukopenia with clozapine and similarly developed these complications with quetiapine in combination with sodium valproate (34).

Arıcı A et al. described, for the first time, a case of a child with autoimmune hemolytic anemia during quetiapine usage (35).

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Tang et al. discussed a case of a patient with hepatocellular carcinoma whose blood test showed neutropenia while using quetiapine (36).

Risperidone

F Mesoten et al. reported the outcome of rising doses of risperidone administered for four weeks to 17 psychiatric patients to assess cardiovascular and hematologic side effects. They observed no severe hematologic side effects at the end of the study (37).

Piperazinyl Phenothiazine

Perphenazine In a study published by Oyewumi, a case of perphenazine-induced aplastic anemia was reported in a 23-year-old male with schizophrenia (38).

Thioxanthene Class

Thiothixene Campbell et al. conducted a trial with ten children aged 3 to 7 years who were hospitalized at Bellevue Hospital due to moderate to severe mental retardation and schizophrenic issues. Based on the psychiatrist's evaluations, one patient developed leukopenia after seven weeks of treatment with thiothixene but returned to normal after six days (39).

Serotonin-Antagonist-and-Reuptake-Inhibitor (SARI)

Trazodone Perry et al. published a clinical trial article discussing the hematological side effects of trazodone after six weeks of treatment. The results showed that patients treated with trazodone experienced a significant decrease in hematocrit, hemoglobin, and red blood cell count, leading to false anemia in 36% of the treated individuals (40).

Anticonvulsant

Sodium Valproate

Vasudev et al. concluded that thrombocytopenia occurs as a side effect of sodium valproate in 5% of female patients. Additionally, sodium valproate may cause an increase in mean corpuscular volume (MCV), especially in the elderly (41).

Zanjani et al., in a review article, studied the hematological toxicity of sodium valproate in children. They found that even in therapeutic doses, sodium valproate can cause severe blood toxicity, including neutropenia, thrombocytopenia, and bone marrow depression (42).

Amitai et al. emphasized the need for periodic monitoring of hematological complications, especially thrombocytopenia, in adolescent psychiatric patients treated with sodium valproate (43).

Baudou et al. reported that two out of 123 infants treated with sodium valproate presented with secondary hematological changes (44).

Tinchon et al. observed significant decreases in neutrophil granulocytes, lymphocytes, and platelets over time in patients treated with sodium valproate (45).

Yoshimura et al. reported decreased platelet count (PLT) in patients receiving VPA [41].

Oh et al. emphasized the hematological complication of neutropenia in children (46).

Richmond et al. documented thrombocytopenia, leukopenia, and neutropenia in a patient who switched from quetiapine to sodium valproate (47).

Kumar et al. reviewed the hematological side effects of sodium valproate (48).

Nasreddine et al. monitored thrombocytopenia in patients (49).

Kim et al. observed thrombocytopenia in 36.7% of critically ill patients under the supervision of the Neurological Intensive Care Unit (NCU) (50).

Carbamazepine

John G et al. described a case of leukopenia and neutropenia after carbamazepine intake (51).

Koutsavlis et al. reported agranulocytosis in a 49-year-old epileptic female taking carbamazepine, which occurred after a sleeve gastrectomy (52).

A case study by A. Avinash et al. highlighted agranulocytosis and Steven Johnson syndrome in a patient taking carbamazepine (53).

Leis et al. documented various blood complications associated with carbamazepine, including thrombocytopenia, hypogammaglobinemia, leukopenia, neutropenia, agranulocytosis, aplastic anemia, red blood cell aplasia, leukemia, and eosinophilia (54).

Kumar et al. reported a case of thrombocytopenia caused by carbamazepine (55).

Chen et al. described a 76-year-old man who developed severe thrombocytopenia 15 days after taking carbamazepine (56).

Subrahmanyam et al. explained the hematological side effects of carbamazepine, including thrombocytopenia, leukopenia, leukocytosis, and eosinophilia (57).

Pellock et al. found that among 4 million patients who used carbamazepine from 1975 to 1986, 923 had serious complications, including 27 cases of aplastic anemia and 10 cases of agranulocytosis (58).

Mood Stabilizers

Lithium

Wessels et al. stated that the most common blood complication associated with lithium use is leukocytosis (58).

Discussion

Blood dyscrasias, including agranulocytosis and aplastic anemia, pose a substantial mortality risk and have been associated with several psychiatric drugs. Notably, mirtazapine, tricyclic antidepressants, mood stabilizers, anticonvulsants, carbamazepine, and conventional antipsychotic agents have been implicated. Additionally, psychiatric medications such as clozapine, while effective in treating schizophrenia, carry potentially life-threatening side effects like agranulocytosis and neutropenia.

To mitigate these risks, diligent safety monitoring is essential. White blood cell monitoring is mandatory in many countries, and various methods exist for assessing blood complications. Parameters such as complete blood count (CBC) and serum drug concentration are routinely checked.

Psychiatrists must not only evaluate multidimensional psychiatric symptoms but also closely monitor patients' physical condition (38). Among psychiatric drugs, clozapine and carbamazepine stand out due to their increased risk of hematological side effects. A study by Gerson et al. reported a fatal case of neutropenic sepsis resulting from combined treatment with clozapine, carbamazepine, lithium, benztropine, and clonazepam (5). Although clozapine and carbamazepine exhibit fewer nonhematological side effects, their hematological risks—especially agranulocytosis—require careful consideration when used in combination.

The literature also highlights hematological inflammatory markers as potential predictors of severe side effects. These markers include the C-reactive protein (CRP) to albumin ratio (CAR), the

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modified Glasgow Prognostic Score (mGPS), the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR). In patients undergoing induction chemotherapy for head and neck cancer, these markers could help anticipate hematological side effects related to psychiatric drugs (6).

Beyond clozapine and carbamazepine, other psychiatric medications, such as antiepileptic drugs, may induce hematological complications. For instance, a study by Sönmez et al. compared the side effects of amitriptyline and mirtazapine in patients with depression and anxiety (7). While both drugs improved depression scores, mirtazapine caused weight gain in more patients, decreased diastolic blood pressure, and led to higher levels of SGPT, cholesterol, and triglycerides compared to amitriptyline. These findings emphasize the need to consider hematological effects alongside cardiovascular and metabolic consequences.

In summary, vigilance regarding hematological side effects is crucial in clinical practice. Regular monitoring of complete blood counts, especially for drugs like clozapine and carbamazepine, remains essential. Balancing the potential risks with therapeutic benefits is critical when initiating or continuing treatment with these agents. Future research should delve into the mechanisms underlying drug-induced hematological alterations and develop strategies to mitigate adverse effects while optimizing psychiatric disorder management.

Study limitations

Small Sample Size: The study's sample size, particularly the subset of patients treated with clozapine and carbamazepine, is relatively small. This limitation may impact the generalizability of the results and the ability to draw definitive conclusions about the prevalence and severity of hematological side effects in a broader population.

Lack of Longitudinal Data

The study's focus on a specific timeframe may restrict the assessment of long-term hematological effects of psychiatric drugs. Longitudinal studies tracking patients over extended periods could provide valuable insights into the persistence and evolution of hematological complications associated with psychiatric pharmacotherapy.

Potential Confounding Factors

The study may not fully account for all potential confounding variables that could influence hematological outcomes, such as concomitant medications, underlying medical conditions, or lifestyle factors. Addressing these confounders through multivariate analysis or subgroup analysis could enhance the study's validity.

Generalizability to Diverse Populations

The study's findings may be limited in their applicability to diverse populations, as patient demographics, comorbidities, and treatment practices can vary significantly across different healthcare settings. Including a more diverse patient population could strengthen the external validity of the study results.

Need for Mechanistic Insights

While the study highlights the occurrence of hematological side effects, it may lack in-depth mechanistic insights into the underlying pathways and interactions leading to these complications.

Future research should aim to elucidate the biological mechanisms driving hematological alterations induced by psychiatric drugs.

Conclusion

The hematological side effects of psychiatric medications, particularly clozapine, and carbamazepine, pose significant clinical challenges, including risks of agranulocytosis, leukopenia, and thrombocytopenia. Regular monitoring of complete blood counts is essential for patients on these drugs to detect early signs of hematological toxicity and to inform patients about symptoms requiring immediate medical attention. The balance between the risks of these side effects and the therapeutic benefits must be carefully considered in treatment decisions.

Further research is needed to explore the long-term effects of chronic methadone therapy on hematological parameters and the role of the gut microbiome in psychopharmacology. Studies have indicated immune system changes associated with chronic methadone use, while the gut-brain axis may influence treatment responses to SSRIs. A proactive approach involving regular monitoring and patient education is crucial for managing the side effects of psychotropic medications effectively.

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