

Mirtazapine induced neutropenia: A case report and systematic review

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Resumen

Introducción. Mirtazapina es un antidepresivo de uso común y que estimula el apetito. A pesar de que en estudios precomercialización la incidencia de neutropenia inducida por mirtazapina fue de 1.1/1000, la literatura sobre este tema es escasa.

Presentación de caso. Una mujer de edad avanzada se presenta inicialmente con neutropenia, sepsis y lesiones vesiculares en piel que no respetan dermatoma luego de 6 meses de haber iniciado mirtazapina. Otras causas probables de su neutropenia y lesiones vesiculares incluyen, entre otros, virus del herpes simplex, virus de varicela zoster, parvovirus, deficiencia de vitamina B12, lupus sistémico eritematoso, los cuales son excluidos como causas probables. Luego de varios estudios, incluida biopsia

de piel, se le diagnostica una agranulocitosis inducida por mirtazapina y foliculitis producida por *S. aureus*. Los neutrófilos se normalizan una vez que la paciente interrumpe la mirtazapina y luego de la administración de factor estimulante de colonias de granulocitos.

Materiales y métodos. PUBMED, EMBASE, Google Scholar y la base de datos CNKI fueron utilizados como motores de búsqueda, y la declaración PRISMA fue utilizada para elaborar el artículo.

Resultados y discusión. 11 estudios y 14 reportes de caso de neutropenia inducida por mirtazapina fueron encontrados en la literatura. Generalmente, el inicio de la neutropenia se dio en semanas a meses de haber empezado la mirtazapina. Se han reportado 2 casos en los que, luego de haber iniciado

nuevamente la mirtazapina, hubo una rápida reducción en el número de neutrófilos debido a la memoria inmunológica. Inhibidores de la recaptación de serotonina e inhibidores de la recaptación de serotonina/noradrenalina fueron administrados de forma segura en 3 casos. El tratamiento es conservador e incluye la interrupción del agente causal.

Abstract

Introduction. Mirtazapine is a commonly used antidepressant with appetite stimulating effects. Although premarketing trials estimate the incidence to be 1.1 per 1000, there is a paucity of literature on this topic.

Case presentation. Elderly female presented with neutropenic sepsis and non-dermatomal vesicular rash around 6 weeks after initiation of mirtazapine. Other causes of neutropenia and rash, including, but not limited to, herpes simplex virus, varicella zoster virus, parvo virus, vitamin B12 deficiency, systemic lupus erythematosus were ruled out. After extensive testing, including skin biopsy, she was diagnosed to have concomitant mirtazapine induced agranulocytosis and staphylococcal folliculitis. Her neutropenia resolved after discontinuation of mirtazapine and administration of G-CSF.

Materials and methodology. Literature search was performed in PUBMED, EMBASE, Google Scholar and CNKI database and manuscript was developed using PRISMA statement and checklist.

Results and discussion. Literature search revealed 11 studies with 14 reported cases of mirtazapine induced neutropenia. Onset of neutropenia on first time exposure was usually within weeks to months. There were two reports of repeat exposure causing rapid drop in ANC due to immunologic memory. SSRIs and SNRIs were safely started in three cases. Treatment is mainly supportive with discontinuation of offending agent.

Introduction

Mirtazapine is a commonly used tetracyclic antidepressant with sedative, anti-emetic and appetite stimulant effects⁽¹⁾. It has a relatively good safety profile with most common adverse effects being drowsiness, hypercholesterolemia and weight gain⁽²⁾. Neutropenia is a rare side effect of mirtazapine. In premarketing clinical trials, the incidence of mirtazapine induced neutropenia was estimated to be

3.1 cases per 1000 to 2.2 cases per 10000⁽²⁾. However, there is remarkably little literature of this condition. We, hereby, present a case report on mirtazapine induced agranulocytosis and perform a systematic review of this topic.

Case report

A 86 year-old Caucasian female with past medical history of dementia, hypothyroidism, paroxysmal atrial fibrillation and chronic kidney disease presented from a nursing home with high grade fever, lethargy and skin rash for two days. She was found to be febrile and hypotensive. She was frail and lethargic. Physical examination revealed irregular rhythm of heart with a systolic murmur, normal breath sounds, non-tender abdomen and a non-dermatomal vesicular rash in bilateral buttocks and lower back.

Laboratory findings revealed white blood cell (WBC) count of $0.3 \times 10^9/L$ (normal range 4 to $11 \times 10^9/L$) with absolute neutrophil count (ANC) of $0 \times 10^9/L$ (normal range 1.5 to $8 \times 10^9/L$), hemoglobin 11g/dL (normal range 12 to 16 g/dL), acute kidney injury (AKI) with creatinine of 1.4 mg/dL with baseline of 0.8 mg/dL, total bilirubin 2.6 (normal range 0.1 to 1.2 mg/dL), alkaline phosphatase of 332 U/L (normal range 44 to 147 U/L), lactate of 2.9 mmol/L (normal range 0 to 2.0 mmol/dL) with normal platelet count, normal aspartate transaminase and alanine transaminase. Chest X-ray demonstrated focal opacity in the right lower lung. She was treated initially as severe sepsis, likely due to pneumonia, with fluid resuscitation and empiric antibiotics. She remained hemodynamically stable after that.

Her blood counts two weeks before were normal and there was no documented episode of neutropenia in the past. She was not on any chemotherapeutic medications. She was started on tablet mirtazapine 7.5 mg daily 6 weeks ago for major depressive disorder, and its dose was increased to 30 mg 4 weeks ago. It was the only new medication she was on. Other home medications included acetaminophen, aspirin, calcium carbonate, senna, levothyroxine, ferrous sulphate, melatonin, multivitamin and polyethylene glycol. The trend of blood counts is shown in figure 1.

Vitamin B12 and folate were normal. Infectious disease workup was negative for Blastomyces antibody, Mycoplasma antibody, Herpes simplex virus 1-2 PCR, Varicella zoster virus PCR, Ehrlichia

chaffeensis antibody, Parvovirus PCR and Human immunodeficiency virus. Blood culture, fungal dimorphic culture and acid fast bacilli culture did not reveal any growth. The culture of skin lesions showed methicillin sensitive *Staphylococcus aureus*. Skin biopsy revealed bacteria and necrotic skin lesions but did not show viral cytopathic effect. Immunohistochemical stain for Herpes simplex virus 1-2 and Varicella zoster virus was negative. Anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. Based on these results, it was concluded that the patient had *Staphylococcus aureus* folliculitis along with mirtazapine induced agranulocytosis.

As the ANC was $0 \times 10^9/L$ without recovery after 3 days of stopping mirtazapine, she was started on G-CSF at dose of 300 micrograms per day for 3 days, which caused ANC to recover to $2.1 \times 10^9/L$. She was discharged back to her nursing home. Complete blood count done a month after discharge showed persistent recovery of ANC ranging between 5.7 to $7.5 \times 10^9/L$.

Materials and methods

Preferred Reporting Items for Systemic review and Meta-Analysis (PRISMA) statement and PRISMA checklist were used for manuscript development⁽³⁾.

Literature search

Literature search was performed in PUBMED, *Google Scholar*, EMBASE and Chinese National Knowledge

Infrastructure (CNKI) database for studies published prior to April, 2023. Search keywords included “mirtazapine”, “remeron”, “neutropenia” and “agranulocytosis”. Boolean search operators “AND” and “OR” were used to link the keywords.

Eligibility criteria

Inclusion criteria include articles with case description of patients with suspected or confirmed mirtazapine induced neutropenia. No language restrictions were applied. Review articles, animal studies and articles which do not meet the criteria of neutropenia were excluded. Neutropenia was defined as ANC less than $1500^{(4)}$. Title and abstracts with or without the full text were screened. Two authors (HK and ZK) screened, retrieved and excluded the studies.

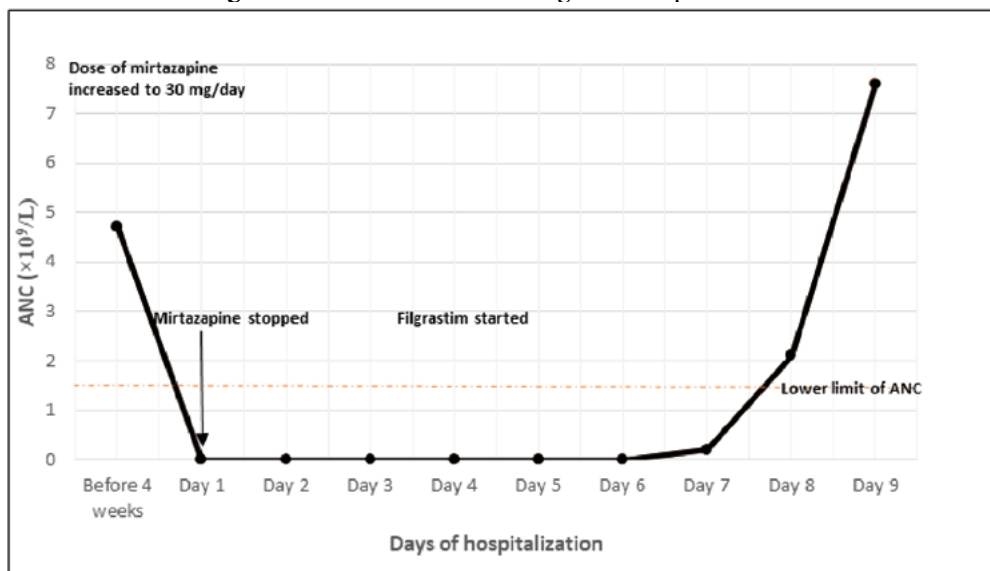
Data extraction

The data extracted included age, sex, time of onset of neutropenia after initiation of drug, initial clinical presentation, dose of mirtazapine used, absolute neutrophil count at nadir, recovery in days, need for cytokine support, outcome of neutropenic episode and antidepressant regimen used in future.

Results

The literature search initially yielded 3060 results in *Google Scholar*, 28 results in PUBMED/MEDLINE, 25 results in EMBASE and 1 result in CNKI database. After excluding the duplicates and those

Figure 1. Trend of ANC throughout hospitalization



not meeting the inclusion criteria, 11 studies were included in our systematic review. The PRISMA flowchart is shown in the figure 2. Three studies⁽⁵⁻⁷⁾ couldn't be retrieved. Four studies⁽⁸⁻¹¹⁾ were excluded because the ANC at nadir was greater than 1500. The eligible case reports are summarized in table 1, while other studies are summarized in table 2.

Discussion

Mirtazapine is a commonly used tetracyclic antidepressant with a good safety profile. With newer immunomodulatory effects of mirtazapine being recently discovered, the use of mirtazapine is expected to increase even more⁽²²⁾. In the aforementioned case, given the temporal relationship of neutropenia with drug, recovery after discontinuation and absence of infectious or autoimmune causes, the diagnosis of mirtazapine induced agranulocytosis was made. Naranjo adverse drug reaction probability scale in our case indicated a probable causal relationship between mirtazapine and neutropenia⁽²³⁾. The skin rash was due to *Staphylococcus aureus* folliculitis.

According to premarketing trials, mirtazapine induced neutropenia occurs in approximately 1.1/1000 patients⁽²⁾. However, this had a very large confidence interval due to its inclusion of only 2796 subjects. Interestingly there is a paucity of literature regarding this condition with only 7 case reports as summarized in table 1 and three in the observational cohort study of mirtazapine prescription event monitoring among 13554 patients for 2 years⁽¹⁹⁾. This relative absence of cases supports the hypothesis that the incidence of mirtazapine induced neutropenia is significantly lower compared to the finding reported by the premarketing trial. However, we have to also consider that frequency reported through case reports may be misleading as it is not compared with the frequency at which the drug is prescribed. In addition, different studies do not have a consistent threshold below which neutropenia is defined and some of the studies, which used higher threshold for definition of neutropenia i.e. greater than 1500/mm³ were excluded from the review. The mechanisms of mirtazapine induced

Figure 2. PRISMA flowchart

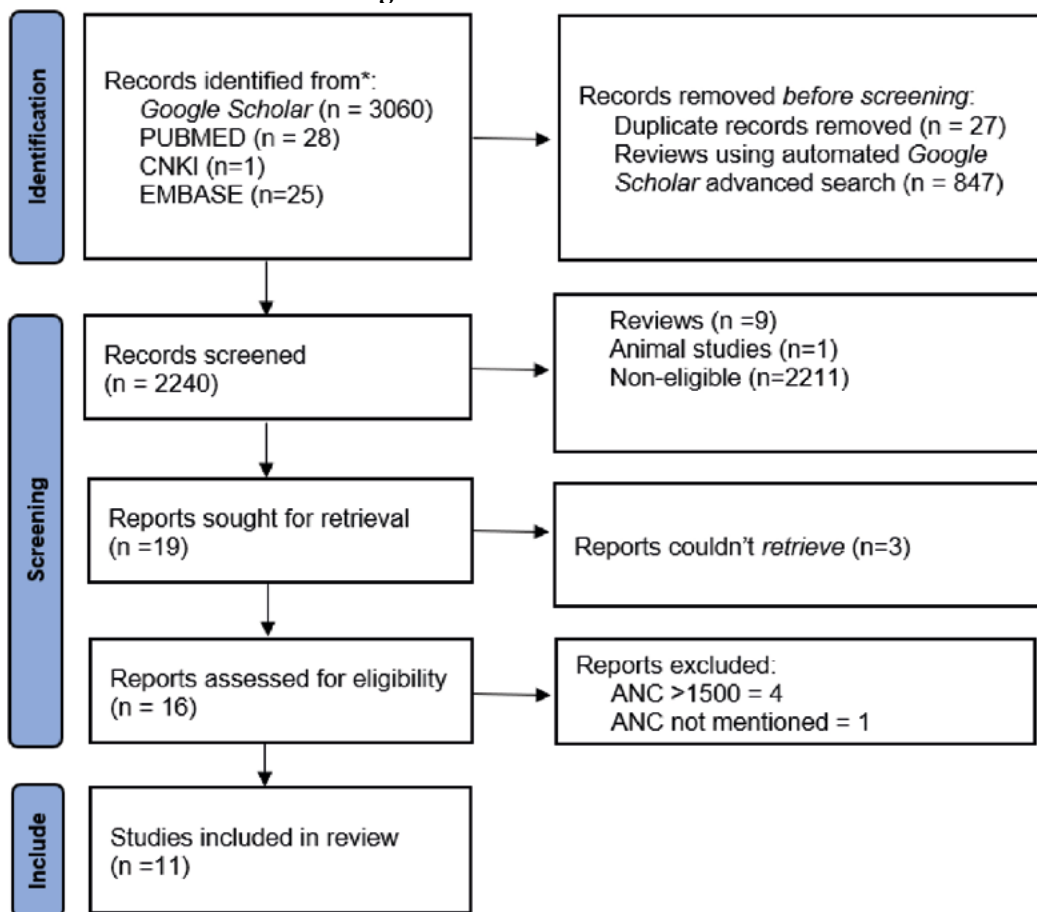


Table 1. Included case studies of mirtazapine induced neutropenia

Author	Onset of neutropenia after initiation of drug	Age	Clinical presentation	ANC at nadir	Dose of mirtazapine	Recovery in days after discontinuation	Need for cytokine support	Antidepressant regimen in the future	Complications	How were other causes ruled out?
Toprak ⁽¹²⁾	10 days	72	Fever and epistaxis	170	15 mg	ANC was 2500 in 21 days	No	Escitalopram	Full recovery	Vitamin B12 and folate were normal. BM biopsy ruled out malignant infiltration.
Anghelescu ⁽¹³⁾	1 day	64	Asymptomatic	300	15 mg	Exact days not given. WBC ranged between 3.5 to 4.2×10 ⁹ /L over 12 months.	No	Venlafaxine	Full recovery	No other tests were performed.
Nazer ⁽¹⁴⁾	Approximately 2 months	40	Febrile neutropenia	18	15 mg	N/A	Filgrastim 300 mcg daily	N/A	Mortality 10 days after admission	HIV, hepatitis C and hepatitis B were ruled out. BM biopsy ruled out malignant infiltration.
Walder ⁽¹⁵⁾	8 months	36	Psychiatric admission (anorexia nervosa)	598	30 mg	Exact days not given, WBC counts had recovered at 8 weeks	No	N/A	Full recovery	Vitamin B12 and folate within normal limits. Bone marrow biopsy not done.
Ozcanli ⁽¹⁶⁾	3 weeks	44	Sore throat with fever	1100	30 mg	2 weeks	No	Sertraline	Full recovery	NA
Civalier ⁽¹⁷⁾	2 days	29	Asymptomatic	530	15 mg	Recovery subjective	No	No	Full recovery	No
Houghan ^(18,p3)	4 weeks	72	Neutropenic fever	160	N/A	3 days	Yes	N/A	Full recovery	N/A

neutropenia are not well known. Just like any other drug mediated neutropenia, the potential causes include immune mediated destruction or direct toxicity⁽²⁴⁾. Typically immune mediated pathophysiology occurs about 1-6 months after initiation of the drug and typically occurs after dose has been increased⁽²⁴⁾. The delay in onset has been hypothesized due to the time it takes for selective T cells to proliferate⁽²⁵⁾. Type 2 and type 4 hypersensitivity have been implicated in immune mediated neutropenia. Testing for anti-drug antibodies may be unnecessary, as the anti-drug antibodies may either be the cause or result of immune mediated injury⁽²⁵⁾. The onset of mirtazapine induced neutropenia ranged from 1 day to 8 months after initiation of the drug with majority of cases occurring within 1 month after initiation of mirtazapine^(2,12,13,16,18).

In two cases, there was a rapid drop of ANC within few days of exposure to mirtazapine. In one of the cas-

es, there was a distant neutropenic episode with amitriptyline and in the other there was a prior neutropenic reaction with mirtazapine itself^(13,17). These may be due to immunologic memory⁽²⁶⁾. Cross reactivity between tricyclic and tetracyclic antidepressants is possible with a few cases reported in the literature⁽²⁷⁾. Review of literature revealed 14 cases of mirtazapine induced neutropenia which has been summarized in tables 1 and 2. In four instances of reported mirtazapine induced neutropenia, the neutrophil count was in a decreasing trend but the definition of neutropenia was not fulfilled with ANC >1500⁽⁸⁻¹¹⁾. There was no specific age predisposition with age ranging from 29 to 72. Three cases^(12,14,16) presented with febrile neutropenia, while other cases were asymptomatic. There was concomitant new onset thrombocytopenia in two cases^(12,15).

Before attributing neutropenia to medication, other potential causes of neutropenia should be excluded,

Table 2. Remainder of included studies

Study	Type of study	Number		Additional comments
Biswas ⁽¹⁹⁾	Observational cohort using mirtazapine prescription event monitoring from 1997 to 1999	13554 patients followed for 2 years	Case 1. Presented with sore throat after 5 months of initiation of mirtazapine. ANC was found to be low but objective ANC not given. Recovery of the counts occurred after stopping the drug. Dose, ANC at nadir and time to recovery not mentioned.	N/A
			Case 2. Presented with abnormal liver function tests and incidental agranulocytosis which resolved after stopping the drug. Dose, duration of use, ANC at nadir and time to recovery not mentioned.	
			Case 3. Myelodysplasia which was detected 5 months after starting mirtazapine resolved on stopping the drug.	
Huber ⁽²⁰⁾	Case control study	51 Berlin hospitals from 2000 to 2010	1 case of probable case of neutropenia d/t mirtazapine. No further details provided.	Patients receiving cytotoxic drug or radiation therapy, or those with congenital agranulocytosis, aplastic anemia, myelofibrosis, neoplastic infiltration of the bone marrow, or vitamin B12 or folic acid deficiency were excluded
Andres ⁽²¹⁾	Retrospective review of cohort	203 cases of drug induced neutropenia from 1984 to 2014	1 case of neutropenia attributed to mirtazapine. No further details provided.	N/A
FDA ⁽²⁾	Premarketing clinical trial	2796	Case 1. Severe neutropenia 61 days after initiation of mirtazapine with recovery after its discontinuation. Dose, ANC at nadir and time to recovery not mentioned.	N/A
			Case 2. Severe neutropenia 9 days after initiation of mirtazapine with recovery after its discontinuation. Dose, ANC at nadir and time to recovery not mentioned.	
			Case 3. Severe neutropenia 14 days after initiation of mirtazapine with recovery after its discontinuation. Dose, ANC at nadir and time to recovery not mentioned.	

first including but not limited to viral infection, vitamin B12, folate, autoimmune workup and ideally a bone marrow biopsy. Such investigations were performed only in 3 cases^(12,14,15) which included bone marrow biopsy in 2 cases^(12,14). Other cases were presumed to be mirtazapine induced neutropenia given the temporal relationship and improvement of counts after discontinuation of the drug^(13,16,17). All

the cases showed full recovery, except for a single case of death secondary to neutropenic sepsis⁽¹⁴⁾.

The treatment is mainly supportive with prompt discontinuation of offending agent as the mainstay of therapy. Only one case required cytokine support with 300 mcg daily of filgrastim⁽¹⁴⁾. Cytokine support in drug induced neutropenia is controversial, with the only randomized controlled trial not show-

ing benefits. However, the limitation in the RCT was lower than usual dose of G-CSF (100-200 microgram per day)⁽²⁸⁾. This is unlike our case where a higher dose of 300 microgram per day was used. However, a systematic review of 980 reported cases found shorter duration of neutropenia and less fatal complications with use of G-CSF⁽²⁹⁾.

Alternate antidepressants from other classes have been reported to be safely initiated in patients with mirtazapine induced neutropenia. There are reports of patients who subsequently tolerated sertraline, escitalopram and venlafaxine well^(12,13,16). However, there was one episode of cross reactivity between

tricyclic and tetracyclic antidepressants⁽²⁷⁾. There were no cross-reactivity events with selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI).

Conclusion

Mirtazapine induced neutropenia is a rare complication of a commonly used drug. It should be considered in the differential of new onset neutropenia. Treatment is mainly supportive, along with discontinuation of the offending agent. G-CSF use can be considered. SSRI and SNRI may be considered in the future, while TCA should be avoided.

Author contributions: HK wrote part of the case report and performed literature search, ZA wrote part of the case report, ZK performed literature search and wrote a part of discussion, EFAS wrote a part of discussion and the summary, BGV helped with literature search, proof reading and edited the manuscript, PAK helped with proof reading and was involved in direct patient care.

Conflictos de intereses: Los autores declaran no poseer conflictos de interés.

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