Management and prevention of agranulocytosis in patients receiving clozapine

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ABSTRACT

Clozapine is an antipsychotic associated with superior efficacy compared to other atypical antipsychotics in the treatment of schizophrenia. However, clozapine use is limited due to its association with a rare but potentially fatal adverse effect, agranulocytosis. Patients receiving clozapine therapy require frequent monitoring of white blood cell (WBC) and absolute neutrophil counts (ANC). This article reviews the monitoring parameters for patients receiving clozapine therapy, and the management and prevention of clozapine-associated agranulocytosis.

KEYWORDS

agranulocytosis, clozapine, prevention, management

INTRODUCTION

Schizophrenia affects approximately 7 out of 1000 adults.[1] More than 50% of people with schizophrenia are not receiving proper pharmacologic and psychosocial therapy.[1] According to The National Institute of Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the drug classes used for the treatment of schizophrenia, first and second generation antipsychotics, are equal in efficacy but differ with regards to their side effect profile and tolerability. The first generation antipsychotics are associated with a higher risk of extrapyramidal side effects (EPS) and the second-generation antipsychotics are associated with a higher risk of metabolic syndrome. Furthermore, the study illustrated that clozapine is significantly more efficacious than the other atypical antipsychotics.[2] One limitation of clozapine is its substantial risk of potentially life-threatening agranulocytosis.[3] Agranulocytosis is characterized by depleted numbers of neutrophils.[4] Agranulocytosis can be managed with hematopoietic growth factors namely, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF).[5]

REVIEW OF CLOZAPINE

Clozapine has demonstrated superior efficacy compared to the other atypical antipsychotics.[2] Clozapine remains the only agent Food and Drug Administration (FDA) approved for treatment resistant schizophrenia and for reduction in recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.[6] Treatment with clozapine has also been shown to result in fewer relapses and lower rates of discontinuation when compared to the other atypical antipsychotics.[6] However, clozapine is associated with a 7% risk of blood dyscrasias.[3,6]

The exact mechanism of action of clozapine is unknown. Clozapine alleviates both positive and negative symptoms of schizophrenia.[7] Some proposed mechanisms of action involve interaction through several dopamine receptor subtypes (D_1, D_2, D_4), noradrenergic and serotoninergic receptors and selective influence on the mesolimbic dopaminergic system.[7] Clozapine exhibits high antagonistic activity towards the D_4 dopamine receptor, 5-HT_{2A} , α_1 and M_1 receptors, whereas the affinity to other members of the dopamine, D_1 and D_2, family, α_2 and 5-HT_{1A} receptors is 10 to 50 times lower.[7] Since the density of D_4 receptors is highest in the frontal cortex and amygdala but relatively low in the basal ganglia, it has been postulated that this contributes to the unique efficacy of clozapine in alleviating symptoms of schizophrenia without causing EPS.[8]

The mechanism of action of clozapine differs slightly from the mechanism of action of other atypical antipsychotics (e.g., risperidone (Risperdal), olanzapine (Zyprexa), and aripiprazole (Abilify). Risperidone has mixed serotonin-dopamine antagonist activity that binds with high affinity to 5-HT_2 receptors in the central nervous system (CNS) and in the periphery nervous system (PNS) and with lower affinity to the dopamine D_2 receptors.[9] The affinity to dopamine-D_2 receptors is 20 times lower than the 5-HT_2 affinity.[9] This is thought to improve negative symptoms of psychosis and reduce the incidence of EPS.[9]

Risperidone also antagonizes the α_1, α_2 adrenergic, and histaminergic receptors with high affinity.[9] Risperidone has low to moderate affinity for 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1A} receptors, weak affinity for D_1 and no affinity for muscarinic or β_1 and β_2 receptors.[9] Olanzapine displays potent antagonism of serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D_{1-4}, histamine H_1 and α_1 adrenergic receptors.[10] Olanzapine shows moderate antagonism of 5-HT_3 and muscarinic M_{1-5} receptors.[10] Olanzapine shows weak antagonism to gamma-aminobutyric acid ($GABA_A$), benzodiazepine (BZD), and β-adrenergic receptors.[10] Aripiprazole functions as a partial agonist at the D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor.[11] Aripiprazole exhibits high affinity for D_2, D_3, 5-HT_{1A}, and 5-HT_{2A} receptors.[11] Aripiprazole displays moderate affinity for D_4, 5-HT_{2C}, 5-HT_7, α_1 adrenergic, and H_1 receptors.[11] Aripiprazole has no affinity for muscarinic receptors.[11]

REVIEW OF AGRANULOCYTOSIS

Agranulocytosis is defined as an absolute neutrophil count (ANC) < 500/mm^3, by white blood cell (WBC) count < 2000/mm^3 and relative lymphopenia. The estimated rate of agranulocytosis in patients taking clozapine ranges from 1-2% after 1 year of therapy and can be fatal if not detected and treated early.[3] Agranulocytosis can initially manifest as a local infection with sore throat, leukoplakia, erythema, and ulceration of the pharynx. These symptoms appear rapidly within days to weeks following initiation of drug therapy.[12]

Baseline WBC count and ANC should be determined prior to initiation of therapy. Clozapine should not be initiated if the baseline WBC count is < 3500/mm^3, ANC is < 2000/mm^3, or the patient has a history of myeloproliferative disorder or previous clozapine-induced agranulocytosis.[3] The FDA suggest all patients treated with clozapine should have weekly WBC and ANC monitoring during the first 6 months of therapy due to a greater risk of developing agranulocytosis (Table 1). From month 7 to 12, WBC and ANC should be monitored every 2 weeks, and then monthly monitoring for the remaining of clozapine therapy if WBC and ANC are normal (Table 1).[3] After discontinuation of therapy, the WBC and ANC should be monitored weekly for at least 4 weeks or until WBC >3500/mm^3 and ANC > 2000/mm^3.[3]

In patients with mild leukopenia (3500/mm^3 > WBC ≥ 3000/mm^3) and/or mild granulocytopenia (2000/mm^3 > ANC ≥ 1500/mm^3), WBC and ANC should be monitored twice weekly until WBC > 3500/mm^3 and ANC > 2000/mm^3.[13] Patients should then be returned to the previous monitoring schedule (Table 2).[13] In patients with moderate leukopenia (3000/mm^3 > WBC ≥ 2000/mm^3) and/or moderate granulocytopenia (1500/mm3 > ANC ≥ 1000/mm^3), therapy should be discontinued.[13] Patients' WBC and ANC should be monitored daily until WBC > 3000/mm^3 and ANC >1500/mm^3.[13] Patients should then be monitored two times per week until WBC > 3500/mm^3 and ANC > 2000/mm^3 (Table 2).[13] Patients can also be rechallenged on clozapine at that point.[13] If patients are rechallenged on clozapine, patients must be monitored weekly for 1 year before returning to the standard monitoring (Table 2).[13] In patients with severe leukopenia (WBC < 2000/mm^3) and/or severe granulocytopenia (ANC < 1000/mm^3), or agranulocytosis (ANC < 500/mm^3), clozapine therapy must be discontinued (Table 2).[13] Patients' WBC and ANC must be monitored daily until WBC > 3000/mm^3 and ANC > 1500/mm^3.[13] Patients must then be monitored two times per week until WBC > 3500/mm^3 and ANC > 2000/mm^3 and weekly thereafter.[13] Patients must be monitored for at least 4 weeks from day of discontinuation of therapy and cannot be rechallenged on clozapine (Table 2).[13]

Table 1. Clozapine WBC/ANC monitoring[3]

	Monitoring frequency	ANC & WBC goals/range
1-6 months	Weekly	WBC 3500/mm^3 & ANC 2000/mm^3
7-12 months	Bi-weekly	WBC 3500/mm^3 & ANC 2000/mm^3
Remainder of therapy	Monthly	WBC 3500/mm^3 & ANC 2000/mm^3
Post therapy- 4 weeks	Weekly	WBC 3500/mm^3 & ANC 2000/mm^3

There are no established risk factors with the development of clozapine-induced agranulocytosis with the exception of evidence of substantial bone marrow suppression during initial therapy.[3] Concomitant administration of drugs associated with agranulocytosis such as carbamazepine, phenobarbital, and phenytoin increases the risk of developing agranulocytosis.[12] Clozapine-induced agranulocytosis occurs more frequently in patients of Eastern European Jewish heritage, most commonly within 4-16 weeks of drug exposures with no dosage or duration of therapy correlation.[3] African descendants, and Middle East descendants are also predisposed to benign ethnic neutropenia, with low leukocyte and neutrophil counts.[14] Approximately 25% to 50% of the population is affected by this condition.[14] A proposed hypothesis of clozapine

Table 2. Clozapine complication monitoring[13]

	Monitoring frequency	WBC & ANC range
Mild leukopenia/mild granulocytopenia	1. Twice-weekly until WBC > 3500/mm3 and ANC > 2000/mm3 2. Then return to previous monitoring frequency	3500/mm3 > WBC ≥ 3000/mm3 & 2000/mm3 > ANC ≥ 1500/mm3
Moderate leukopenia/ moderate granulocytopenia	1. Hold therapy 2. Daily until WBC > 3000/mm3 and ANC >1500/mm3 3. Twice-weekly until WBC > 3500/mm3 and ANC > 2000/mm3 4. May rechallenge when WBC > 3500/mm3 and ANC > 2000/mm3 5. If rechallenged, monitor weekly for 1 year before returning to standard monitoring schedule	3000/mm3 > WBC ≥ 2000/mm3 & 1500/mm3 > ANC ≥ 1000/mm3
Severe leukopenia/ severe granulocytopenia	1. Discontinue treatment and do not rechallenge patient 2. Daily until WBC > 3000/mm3 and ANC > 1500/mm3 3.Twice weekly until WBC > 3500/mm3 and ANC > 2000/mm3 4. Weekly after WBC > 3500/mm3 5. Must monitor for at least four weeks from day of discontinuation of therapy	WBC < 2000/mm3 & ANC < 1000/mm3
Agranulocytosis	1. Discontinue treatment and do not rechallenge patient 2. Daily until WBC > 3000/mm3 and ANC > 1500/mm3 3. Twice weekly until WBC > 3500/mm3 and ANC > 2000/mm3 4. Weekly after WBC > 3500/mm3 5. Must monitor for at least four weeks from day of discontinuation of therapy	ANC < 500/mm3

induced agranulocytosis is that the toxic effects from the formation of a nitrenium ion on the leukocytes causes acceleration of the physiologic cell death cycle.[8,12] Unstable reactive metabolites of clozapine produce oxidative stress in neutrophils that accelerate the brief life cycle of leukocytes (normal life span 8-12 hours).[8] Clozapine undergoes bioactivation by P450 and peroxidase enzymes to form the toxic and reactive nitrenium ion.[15] This unstable metabolite covalently binds to cellular proteins, depletes intracellular glutathione (GSH) and lead to polymorphonuclear and mononuclear cell toxicity.[15] In patients who receive chronic clozapine therapy, it is possible that haptenation of polymorphonuclear cells occurs and that they may become depleted of glutathione, leading to apoptosis.[15]

PREVENTION AND TREATMENT OF CLOZAPINE ASSOCIATED AGRANULOCYTOSIS

The monitoring parameters previously discussed are the main strategy for the prevention of clozapine associated neutropenia. In addition to routine WBC and ANC monitoring, there are also pharmacologic mechanisms that have been utilized, namely lithium carbonate and granulocyte colony-stimulating factors, to allow clozapine to be used in patients with high risk factors or current neutropenia. Lithium is used in these patients due to its ability to increase the production of granulocytes. It does this by up-regulating granulopoiesis stimulation factors. This side effect of lithium can occur when the serum concentration is between 0.4 mEq/L and 1.1 mEq/L.[18] The neutrophilia caused by lithium does not appear to be dose related; however, a minimum serum concentration (i.e., 0.4 mEq/L) may be required to observe this effect.[17] The increase in WBC count with lithium is expected to between 30% and 45% greater than pretreatment levels, although this increase is reversible upon discontinuation of lithium.[19] While lithium is not FDA approved for this indication, its use as adjunct treatment to clozapine or as pre-treatment has been described in several case reports of both adult and pediatric patients. Silverstone describes a case of a 29-year-old male with a 9-year history of schizophrenia.[18] The patient was being successfully treated with clozapine; however, it had to be discontinued secondary to his low granulocyte count (1.4 x 109 /L). After trials of several other antipsychotics this patient was pre-treated with lithium for 3 weeks to allow for the re-initiation of clozapine. Throughout the re-introduction and treatment with clozapine, his WBC remained stable.[18] Similar results are reported by Blier et al. who describes two case reports in which lithium was used to increase the WBC after patients developed decreased WBC and neutrophils.[20] Each patient was

initiated with lithium 600 mg at bedtime (lithium was increased to 600 mg twice daily in one patient). Over the course of at least 3 days, their WBC and neutrophils began to increase.[20] Benign ethnic neutropenia (BEN) may be described as a baseline neutrophil count less than 1500/ml in the absence of a history of susceptibility to infection in persons of African descent and other ethnic groups of the Middle East.[21] As a result of BEN, clozapine may be under prescribed in this patient population.

There are case reports of lithium use in patients with BEN used to allow for the continuation or initiation of clozapine. Pinninti et al describes the case of a 51 year old African American male diagnosed with schizoaffective disorder, bipolar type, and alcohol abuse.[22] Over the course of two years, the patient experienced multiple relapses of manic episodes. Several pharmacologic trials were unsuccessful in preventing the relapses. Clozapine was then considered; however, the patient had a baseline WBC of 4.1 x 10^3/microL and an ANC of 1.9x10^3/microL. With the initiation of clozapine, the ANC and WBC dropped to 1.0x10^3/microL and 3.4x10^3/microL. Lithium carbonate 300 mg/day was added to his regimen at which point the ANC and WBC increased to 2.2x10^3/microL and 4.1x10^3/microL, respectively. Lithium and clozapine were further increased to 600 mg/day and 150 mg/day, respectively. This patient was maintained on this regimen and was eventually able to be discharged after a period of 34 months.[22] Nykiel et al. describes a similar case in which the patient was a 40 year old African immigrant diagnosed with paranoid schizophrenia.[23] After several trials of antipsychotics, he was initiated on clozapine and titrated to 150 mg/day. His initial ANC and WBC were 2.1 mm^3 and 4.8 mm^3, respectively. With the initiation of clozapine his ANC continued to remain low, even with a decrease in clozapine to 100 mg/day. He was diagnosed with BEN. Secondary to his continued symptoms clozapine was increased to 150 mg/day again at which point his ANC was on average 1.98 mm^3. Lithium was started at 300 mg twice daily and increased to 900 mg/day after 8 weeks. After the initiation of lithium his ANC averaged 2.8 mm^3.[23]

With regards to this off label indication (granulopoiesis) lithium is often preferred over granulocyte colony-stimulating factors due to its lower cost and ease of administration. The use of lithium may also be beneficial not only for its granulopoiesis activity but also for its mood stabilizing effects in patients with bipolar disorder.[17] The use of lithium for this indication has its limitations. Patients receiving lithium in combination with clozapine may be at risk for lithium toxicity despite maintaining lithium within a normal therapeutic range. This has been reported in up to 20% of patients receiving the combination therapy.[17] Lithium also does not prevent clozapine-induced agranulocytosis from occurring in all cases. There are reports of agranulocytosis occurring in patients despite being treated with concurrent lithium.[17,18] Neurologic adverse effects associated with the use of lithium and clozapine combined include tremors, involuntary jerking, stumbling gait, and seizures. Reports of these neurologic adverse events were associated with the use of higher doses of clozapine. These adverse effects are said to be reversible and may occur at normal lithium concentrations when lithium is combined with an antipsychotic.[19]

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are used to treat neutropenic conditions. G-CSFs marketed in the U.S. include filgrastim (Neupogen) and pegfilgrastim (Neulasta). GM-CSFs marketed in the U.S. include sargramostim (Leukine). They each have the ability to stimulate the proliferation and differentiation of myeloid precursor cells in the bone marrow and have been used in the treatment of clozapine induced agranulocytosis. G-CSF and GM-CSF have been shown to decrease the recovery time associated with agranulocytosis.[16,24] There is not a well-defined established dose for agranulocytosis secondary to clozapine; however, they are each normally administered subcutaneously in doses of 4-10 micrograms/kg/day and discontinued 24 hours after the absolute neutrophil count is > 500/mm^3.[16] Khan et al. describes three cases of male patients in their 20's or 30's diagnosed with schizophrenia.[25] Each patient received clozapine which had to be discontinued secondary to neutropenia. After trials of other antipsychotic medications, each patient was re-tried on clozapine. They each received 30 million units of filgrastim, prior to re-treatment with clozapine which increased their neutrophil count high enough to be re-started and maintained on clozapine. The maintenance use of filgrastim in each patient varied. One patient was able to receive a single dose of filgrastim while the other two continued to be maintained on combination therapy.[25] G-CSF and GM-CSF are not FDA approved for this indication and are associated with adverse effects. At high doses GM-CSF is associated with bone pain, erythroderma, weight gain, edema, and other inflammatory problems. G-CSF is generally well tolerated, but may be associated with allergic reactions, bone pain, enlarged spleen, hepatomegaly, urinary abnormalities, and splenic rupture (which is rare). The benefits must outweigh the risks and if either treatment is used it should be done with supervision/collaboration from a haematologist.[25,26]

CONCLUSION

Clozapine is an atypical antipsychotic associated with superior efficacy with regards to its use in schizophrenia. Clozapine is also associated with a rare but potentially fatal adverse effect, agranulocytosis. Secondary to this adverse effect clozapine monitoring is required in patients being treated with clozapine throughout the duration of their therapy. While there is no FDA approved treatment for clozapine induced agranulocytosis, pharmacologic methods have been utilized in clinical practice. These include lithium and granulocyte colony stimulating factor. The use of lithium and granulocyte colony stimulating factor has been shown to be beneficial in this patient population primarily through case studies. Each of these pharmacologic methods is associated with both benefits and risk; these must be weighed when considering whether to re-challenge a patient that has experienced neutropenia associated with clozapine use. In the discussed case studies, patients who were re-challenged with clozapine while receiving pre-treatment and/or combination treatment with lithium or colony stimulating factor were each patients who had shown a particular benefit to the use of clozapine. Lithium and/or colony stimulating factor should be considered for this off label use when other options for the treatment of the patient have been exhausted (i.e., a trial of other antipsychotics).One must use their clinical judgment to determine if the benefits of use outweigh the risk. Other factors to consider when deciding on whether to use lithium or colony stimulating factor include the adverse effects of each, monitoring parameters associated with their use, and cost. If a patient develops agranulocytosis, the appropriate steps should be taken to decrease the risk of adverse outcomes.

REFERENCES

1. World Health Organization. Schizophrenia. Available at. http://www.who.int/mental_health/management/schizophrenia/en/ Accessed June 5, 2013.
2. Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull. 2003;29(1):15-31. PubMed PMID: 12908658.
3. Clozaril [package insert]. East Hanover, New Jersey: Novartis;2013
4. PubMed Health. Agranulocytosis. Available at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002272/#.UbUa5DOn4KE.email. Accessed June 5, 2013.
5. Vial T, Gallant C, Choqu-Kastylevsky G, Descotes J. Treatment of drug-induced agranulocytosis with haematopoietic growth factors: a review of the clinical experience. BioDrugs. 1999;11(3):185-200. PubMed PMID: 18031129.
6. Masand PS. Differential pharmacology of atypical antipsychotics: clinical implications. Am J Health Syst Pharm. 2007;64(2 Suppl 1):S3-8; quiz S24-5. DOI: 10.2146/ajhp060593. PubMed PMID: 17215475.
7. Brunello N, Masotto C, Steardo L, Markstein R, Racagni G. New insights into the biology of schizophrenia through the mechanism of action of clozapine. Neuropsychopharmacology. 1995;13(3):177- 213. DOI: 10.1016/0893-133X(95)00068-O.
8. Robinson D. Psychopharmacology research tutorial for practitioners. Clozapine agranulocytosis: mechanism of drug toxicity. Prim Psychiatry. 2006;13(3):27-29.
9. Risperidone. In: Lexi-drugs . Hudson, OH. Lexi-Comp, Inc.(Accessed 2013 Aug 17)
10. Olanzapine. In: Lexi-drugs . Hudson, OH. Lexi-Comp, Inc.(Accessed 2013 Aug 17)
11. Aripiprazole. In: Lexi-drugs . Hudson, OH. Lexi-Comp, Inc.(Accessed 2013 Aug 17)
12. Hansen CN, Rosenberg AF. Chapter 112. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York: McGraw-Hill; 2011. http://www.accesspharmacy.com/content.aspx?aID=8000685.
13. Food and Drug Administration. Important Drug Warning and New Information. Available at : http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153074.pdf. Accessibility verified August 17, 2013.
14. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? J Lab Clin Med. 1999;133(1):15-22. DOI: 10.1053/lc.1999.v133.a94931. PubMed PMID: 10385477.
15. Bhatt V, Saleem A. Review: Drug-induced neutropenia--pathophysiology, clinical features, and management. Ann Clin Lab Sci. 2004;34(2):131-7. PubMed PMID: 15228223.
16. Esposito D, Rouillon F, Limosin F. Continuing clozapine treatment despite neutropenia. Eur J Clin Pharmacol. 2005;60(11):759-64. DOI: 10.1007/s00228-004-0835-z. PubMed PMID: 15660271.
17. Paton C. Managing clozapine-induced neutropenia with lithium. Psychiatric Bulletin. 2005;29(5):186- 188. DOI: 10.1192/pb.29.5.186.
18. Silverstone PH. Prevention of clozapine-induced neutropenia by pretreatment with lithium. J Clin Psychopharmacol. 1998;18(1):86-8. PubMed PMID: 9472850.
19. Whiskey E, Taylor D. Restarting clozapine after neutropenia: evaluating the possibilities and practicalities. CNS Drugs. 2007;21(1):25-35. PubMed PMID: 17190527.
20. Blier P, Slater S, Measham T, Koch M, Wiviott G. Lithium and clozapine-induced neutropenia/agranulocytosis. Int Clin Psychopharmacol. 1998;13(3):137-40. PubMed PMID: 9690982.
21. Ghaznavi S, Nakic M, Rao P, Hu J, Brewer JA, Hannestad J, et al. Rechallenging with clozapine following neutropenia: treatment options for refractory schizophrenia. Am J Psychiatry. 2008;165(7):813-8. DOI: 10.1176/appi.ajp.2008.07111823. PubMed PMID: 18593787.
22. Pinninti NR, Houdart MP, Strouse EM. Case report of long-term lithium for treatment and prevention of clozapine-induced neutropenia in an African American male. J Clin Psychopharmacol. 2010;30(2):219-21. DOI: 10.1097/JCP.0b013e3181d47b74. PubMed PMID: 20520308.
23. Nykiel S, Henderson D, Bhide G, Freudenreich O. Lithium to allow clozapine prescribing in benign ethnic neutropenia. Clin Schizophr Relat Psychoses. 2010;4(2):138-40. DOI: 10.3371/CSRP.4.2.5. PubMed PMID: 20643636.
24. Mathewson KA, Lindenmayer JP. Clozapine and granulocyte colony-stimulating factor: potential for long-term combination treatment for clozapine-induced neutropenia. J Clin Psychopharmacol. 2007;27(6):714-5.
25. Khan AA, Harvey J, Sengupta S. Continuing clozapine with granulocyte colony-stimulating factor in patients with neutropenia. Ther Adv Psychopharmacol. 2013;3(5):266-71. DOI: 10.1177/2045125313476877. PubMed PMID: 24167701; PubMed Central PMCID: PMC3805383.
26. Wadhwa M, Thorpe R. Haematopoietic growth factors and their therapeutic use. Thromb Haemost. 2008;99(5):863-73. PubMed PMID: 18449415.
27. Kohnle D. (2012). Agranulocytosis. Retrieved from http://www.med.nyu.edu/content?ChunkIID=179519 Accessed June 14, 2013

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