

Neutropenia and Leukopenia After Cross Taper From Quetiapine to Divalproex for the Treatment of Borderline Personality Disorder

Caroline Richmond, PharmD, BCPP^a; and Stephanie Coveart, PharmD, BCPS, BCPP^{a,b}

Background: Valproic acid (VPA) and its derivative, divalproex (DVP) can cause various hematologic dyscrasias, the most common being thrombocytopenia. Neutropenia and leukopenia have been reported in isolated cases, most occurring in pediatric patients or patients with epilepsy. We report a case of leukopenia and neutropenia that presented after cross taper from quetiapine to DVP for the treatment of borderline personality disorder.

Case presentation: A 34-year-old male patient with history of posttraumatic stress disorder, opioid use disorder, alcohol use disorder, stimulant use disorder, cannabis use, and borderline personality disorder underwent a cross taper from quetiapine to divalproex (DVP). DVP was titrated to 1000 mg per day, complete blood count (CBC) was obtained after completion of cross taper and revealed neutropenia and leukopenia with

no documented history of blood dyscrasias. Nine days after discontinuation of DVP, neutrophil and white blood cell count returned to normal limits. With a score of 7 on the Naranjo Adverse Drug Reaction Probability Scale, an adverse reaction of probable DVP-induced neutropenia was documented and medication was not resumed.

Conclusions: This case suggests that there may be a correlation between DVP and isolated neutropenia and leukopenia. Although a CBC is collected routinely to monitor for thrombocytopenia, health care practitioners also should consider other blood dyscrasias. Further studies are warranted to determine incidence of neutropenia and leukopenia with DVP therapy and evaluate whether the medication can be safely continued in cases of mild-to-moderate neutropenia with close monitoring.

Author affiliations can be found at the end of this article.

Correspondence:

Caroline Richmond
(caroline.richmond@va.gov)

Fed Pract. 2022;39(4).

Published online April 11.

doi:10.12788/fp.0247

Valproic acid (VPA) and its derivative, divalproex (DVP) are prescribed for a variety of indications, commonly for seizure control in patients with epilepsy, mood stabilization in patients with bipolar disorder, and migraine prophylaxis. Gastrointestinal distress and sedation are among the most reported adverse effects (AEs) with DVP therapy.¹ Although serious hepatic and hematologic AEs are rare, monitoring is still recommended. DVP can cause various hematologic dyscrasias, the most common being thrombocytopenia.^{1,2} Neutropenia and leukopenia have been reported in isolated cases, most occurring in pediatric patients or patients with epilepsy.³⁻¹⁴

Several case reports of DVP-related neutropenia (absolute neutrophil count [ANC] < 1.50 10³/mcL) and leukopenia (white blood cell count [WBC] < 4.0 10³/mcL) were reviewed during our literature search, some caused by DVP monotherapy; others were thought to be related to concomitant use of DVP and another drug.¹⁵⁻²⁵ Quetiapine was the antipsychotic most commonly implicated in causing hematologic abnormalities when combined with DVP. We report a case of neutropenia and leukopenia that presented after a cross taper from quetiapine to DVP for the treatment of border-

line personality disorder (BPD).

Although no medications have been approved by the US Food and Drug Administration (FDA) for the treatment of BPD, mood stabilizers, including DVP, have literature to support their use for the treatment of affective dysregulation and impulsive behavioral dyscontrol.²⁶⁻²⁸ A therapeutic range for DVP in the treatment of BPD has not been defined; therefore, for this case report, the generally accepted range of 50 to 100 µg/mL will be considered therapeutic.¹

CASE PRESENTATION

A 34-year-old male patient presented to the mental health clinic pharmacist reporting that his current psychotropic medication regimen was not effective. His medical history included posttraumatic stress disorder (PTSD), opioid use disorder, alcohol use disorder, stimulant use disorder, cannabis use, BPD, hypertension, hyperlipidemia, prediabetes, gastroesophageal reflux disease, and a pulmonary nodule. On initial presentation, the patient was prescribed buprenorphine 24 mg/naloxone 6 mg, quetiapine 400 mg, duloxetine 120 mg, and prazosin 15 mg per day. At the time of pharmacy consultation, last reported alcohol or nonprescribed opioid use was about 6 months prior, and

TABLE Laboratory Results

Variables	6 Mo Before DVP Initiation	3 Mo Before DVP Initiation	1 Wk After Stable DVP Dosing	1 Wk After DVP Discontinuation	Reference Range
White blood cell, 10 ³ /mcL	6.63	6.18	3.51 ^a	5.80	4.00-10.00
ANC, 10 ³ /mcL	3.55	3.37	1.00 ^a	2.78	1.50-7.40
Neutrophil, %	53.5	54.5	28.4 ^a	47.9	38-72
Platelet, 10 ³ /mcL	197	232	169	223	150-420
Hemoglobin, g/dL	13.3 ^a	13.4 ^a	12.5 ^a	12.0 ^a	13.5-17.0
Hematocrit, %	41.5	40.8	39.5 ^a	37.5 ^a	40-51
Valproic acid, mcg/mL	-	-	28.74	-	50-100

Abbreviations: ANC, absolute neutrophil count; DVP, divalproex.

^aBelow reference range.

methamphetamine use about 1 month prior, with ongoing cannabis use. The patient had a history of participating in cognitive processing therapy, dialectical behavior therapy (DBT), and residential treatment for both PTSD and substance use. Additionally, he was actively participating in contingency management for stimulant use disorder and self-management and recovery training group.

The patient reported ongoing mood lability, hypervigilance, and oversedation with current psychotropic regimen. The prescriber of his medication for opioid use disorder also reported the patient experienced labile mood, impulsive behavior, and anger outbursts. In the setting of intolerability due to oversedation with quetiapine, cardiometabolic risk, and lack of clear indication for use, the patient and health care practitioner (HCP) agreed to taper quetiapine and initiate a trial of DVP for affective dysregulation and impulsive-behavioral dyscontrol. To prevent cholinergic rebound and insomnia with abrupt discontinuation of quetiapine, DVP and quetiapine were cross tapered. The following cross taper was prescribed: quetiapine 300 mg and DVP 500 mg per day for week 1; quetiapine 200 mg and DVP 500 mg per day for week 2; quetiapine 100 mg and DVP 1000 mg per day for week 3; quetiapine 50 mg and DVP 1000 mg per day for week 4; followed by DVP 1000 mg per day and discontinuation of quetiapine.

During a 4-week follow-up appointment,

the patient reported appropriate completion of cross taper but stopped taking the DVP 3 days prior to the appointment due to self-reported lack of efficacy. For this reason, serum VPA level was not obtained. After discussion with his HCP, the patient restarted DVP 1000 mg per day without retitration with plans to get laboratory tests in 1 week. The next week, laboratory tests were notable for VPA level 28.74 (reference range, 50-100) µg/mL, low WBC 3.51 (reference range, 4.00-10.00) 10³/mcL, platelets 169 (reference range, 150-420) 10³/mcL, and low ANC 1.00 (reference range, 1.50-7.40) 10³/mcL (Table). This raised clinical concern as the patient had no history of documented neutropenia or leukopenia, with most recent complete blood count (CBC) prior to DVP initiation 3 months earlier while prescribed quetiapine.

On further review, the HCP opted to cease administration of DVP and repeat CBC with differential in 1 week. Nine days later, laboratory tests were performed and compared with those collected the week before, revealing resolution of neutropenia and leukopenia. A score of 7 on the Naranjo Adverse Drug Reaction Probability Scale (NADRPS) was determined based on previous conclusive reports on the reaction (+1), appeared after suspected drug administration (+2), improved with drug discontinuation (+1), confirmed by objective evidence (+1), and no alternative causes could be found (+2).²⁹ With a

NADRPS score of 7, an AE of probable DVP-induced neutropenia was documented and medication was not resumed.

DISCUSSION

Our case report describes isolated neutropenia and leukopenia that developed after a cross taper from quetiapine to DVP. Hematologic abnormalities resolved after discontinuation of DVP, suggesting a likely correlation. DVP has a well-established, dose-related prevalence of thrombocytopenia occurring in up to 27% of patients.¹ Fewer case reports exist on neutropenia and leukopenia. DVP-induced neutropenia is thought to be a result of direct bone marrow suppression, whereas the more commonly occurring blood dyscrasia, thrombocytopenia, is thought to be caused by an antibody-mediated destruction of platelets.⁶

Management of DVP-induced thrombocytopenia is often dependent on the severity of the reaction. In mild-to-moderate cases, intervention may not be necessary as thrombocytopenia has been shown to resolve without adjustment to DVP therapy.¹ In more severe or symptomatic cases, dose reduction or discontinuation of the offending agent is recommended, typically resulting in resolution shortly following pharmacologic intervention.

Guidance on the management of other drug-induced hematologic abnormalities, such as neutropenia and leukopenia are not as well established. A 2019 systematic review of idiosyncratic drug-induced neutropenia suggested that continuing the offending drug with strict monitoring could be considered in cases of mild neutropenia. In cases of moderate neutropenia, the author suggests temporary cessation of the drug and reinstatement once neutrophil count normalizes and definitive cessation of the drug in severe cases.³⁰

In our case, continuing the offending agent with close monitoring was considered, similar to the well-established management of clozapine-induced neutropenia. However, due to the concern that the ANC was bordering moderate neutropenia in the absence of a therapeutic VPA level as well as a significant reduction in platelets, although not meeting criteria for thrombocytopenia, the decision was made to err on the side of caution and discontinue the most likely offending agent.

It is important to highlight that DVP was replacing quetiapine in the form of a cross taper. Quetiapine is structurally similar to clozapine. While clozapine has strict monitoring requirements related to neutropenia, blood dyscrasias with quetiapine therapy are rare. Quetiapine-induced hematologic abnormalities may be due to direct toxicity or to an immune-mediated mechanism, leading to bone marrow suppression.²⁰ Case reports documenting blood dyscrasias with the combination of DVP and quetiapine were identified during literature review.¹⁵⁻¹⁹ Despite these case reports, we believe DVP was the primary offending agent in our case as the patient's last dose of quetiapine was 2 weeks before obtaining the abnormal CBC. There was no history of blood dyscrasias with quetiapine monotherapy; however, the effect of the combination of DVP and quetiapine is unknown as no CBC was obtained during the cross-taper period.

Although there are no FDA-approved medications for the treatment of BPD, mood stabilizers, including DVP, have some research to support their use for the treatment of affective dysregulation and impulsive-behavioral dyscontrol.²⁶⁻²⁸ In our case, DVP was selected due to the evidence for use in BPD and ability to assess adherence with therapeutic monitoring. Although polypharmacy is a concern in patients with BPD, in our case we believed that the patient's ongoing mood lability and impulsive behaviors warranted pharmacologic intervention. Additionally, DVP provided an advantage in its ability to quickly titrate to therapeutic dose when compared with lamotrigine and a lower risk of cognitive AEs when compared with topiramate.

CONCLUSIONS

To our knowledge, this case report demonstrates the first published case of neutropenia and leukopenia related to DVP therapy for the treatment of BPD. Routine CBC monitoring is recommended with DVP therapy, and our case highlights the importance of evaluating for not only thrombocytopenia, but also other blood dyscrasias during the titration phase even in the absence of a therapeutic VPA level. Further studies are warranted to determine incidence of DVP-related neutropenia and

leukopenia and to evaluate the safety of continuing DVP in cases of mild-to-moderate neutropenia with close monitoring.

Author affiliations

^aMemphis Veterans Affairs Medical Center, Tennessee
^bUniversity of Tennessee College of Pharmacy, Memphis

Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

Ethics and consent

The authors report that the patient provided verbal informed consent. Patient information has been changed to avoid identification.

References

- Depakote (valproic acid). Package insert. Abbott Laboratories; June 2000.
- Conley EL, Coley KC, Pollock BG, Dapos SV, Maxwell R, Branch RA. Prevalence and risk of thrombocytopenia with valproic acid: experience at a psychiatric teaching hospital. *Pharmacotherapy*. 2001;21(11):1325-1330. doi:10.1592/phco.21.17.1325.34418
- Jaeken J, van Goethem C, Casaer P, Devlieger H, Eggermont E, Pilet M. Neutropenia during sodium valproate therapy. *Arch Dis Child*. 1979;54(12):986-987. doi:10.1136/adc.54.12.986
- Barr RD, Copeland SA, Stockwell MC, Morris N, Kelton JC. Valproic acid and immune thrombocytopenia. *Arch Dis Child*. 1982;57(9):681-684. doi:10.1136/adc.57.9.681
- Symon DNK, Russell G. Sodium valproate and neutropenia (letter). *Arch Dis Child*. 1983;58:235. doi:10.1136/adc.58.3.235
- Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr*. 1990;117(3):495-499. doi:10.1016/s0022-3476(05)81105-9
- Blackburn SC, Oliart AD, García-Rodríguez LA, Pérez Gutthann S. Antiepileptics and blood dyscrasias: a cohort study. *Pharmacotherapy*. 1998;18(6):1277-1283.
- Acharya S, Bussell JB. Hematologic toxicity of sodium valproate. *J Pediatr Hematol Oncol*. 2000;22(1):62-65. doi:10.1097/00043426-200001000-00012
- Vesta KS, Medina PJ. Valproic acid-induced neutropenia. *Ann Pharmacother*. 2003;37(6):819-821. doi:10.1345/aph.1C381
- Kohli U, Gulati, S. Sodium valproate induced isolated neutropenia. *Indian J Pediatr*. 2006;73(9):844-844. doi:10.1007/BF02790401
- Hsu HC, Tseng HK, Wang SC, Wang YY. Valproic acid-induced agranulocytosis. *Int J Gerontol*. 2009;3(2):137-139. doi:10.1016/S1873-9598(09)70036-5
- Chakraborty S, Chakraborty J, Mandal S, Ghosal MK. A rare occurrence of isolated neutropenia with valproic acid: a case report. *J Indian Med Assoc*. 2011;109(5):345-346.
- Stoner SC, Deal E, Lurk JT. Delayed-onset neutropenia with divalproex sodium. *Ann Pharmacother*. 2008;42(10):1507-1510. doi:10.1345/aph.1L239
- Storch DD. Severe leukopenia with valproate. *J Am Acad Child Adolesc Psychiatry*. 2000;39(10):1208-1209. doi:10.1097/00004583-200010000-00003
- Rahman A, Mican LM, Fischer C, Campbell AH. Evaluating the incidence of leukopenia and neutropenia with valproate, quetiapine, or the combination in children and adolescents. *Ann Pharmacother*. 2009;43:822-830. doi:10.1345/aph.1L617
- Hung WC, Hsieh MH. Neutropenia associated with the comedication of quetiapine and valproate in 2 elderly patients. *J Clin Psychopharmacol*. 2012;32(3):416-417. doi:10.1097/JCP.0b013e3182549d2d
- Park HJ, Kim JY. Incidence of neutropenia with valproate and quetiapine combination treatment in subjects with acquired brain injuries. *Arch Phys Med Rehabil*. 2016;97(2):183-188. doi:10.1016/j.apmr.2015.09.004
- Estabrook KR, Pheister M. A case of quetiapine XR and divalproex-associated neutropenia followed by successful use of ziprasidone. *J Clin Psychopharmacol*. 2012;32(3):417-418. doi:10.1097/JCP.0b013e318253a071
- Nair P, Lippmann S. Is leukopenia associated with divalproex and/or quetiapine? *Psychosomatics*. 2005;46(2):188-189. doi:10.1176/appi.psy.46.2.188
- Cowan C, Oakley C. Leukopenia and neutropenia induced by quetiapine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(1):292-294. doi:10.1016/j.pnpbp.2006.07.003
- Fan KY, Chen WY, Huang MC. Quetiapine-associated leukopenia and thrombocytopenia: a case report. *BMC Psychiatry*. 2015;15:110. doi:10.1186/s12888-015-0495-9
- Malik S, Lally J, Ajnakina O, et al. Sodium valproate and clozapine induced neutropenia: A case control study using register data. *Schizophr Res*. 2018;195:267-273. doi:10.1016/j.schres.2017.08.041
- Pantelis C, Adesanya A. Increased risk of neutropenia and agranulocytosis with sodium valproate used adjunctively with clozapine. *Aust N Z J Psychiatry*. 2001;35(4):544-545. doi:10.1046/j.1440-1614.2001.09111.x
- Madeb R, Hirschmann S, Kurs R, Turkie A, Modai I. Combined clozapine and valproic acid treatment-induced agranulocytosis. *Eur Psychiatry*. 2002;17(4):238-239. doi:10.1016/s0924-9338(02)00659-4
- Dose M, Hellweg R, Yassouridis A, Theison M, Emrich HM. Combined treatment of schizophrenic psychoses with haloperidol and valproate. *Pharmacopsychiatry*. 1998;31(4):122-125. doi:10.1055/s-2007-979312
- Ingenhoven T, Lafay P, Rinne T, Passchier J, Duivenvoorden H. Effectiveness of pharmacotherapy for severe personality disorders: meta-analyses of randomized controlled trials. *J Clin Psychiatry*. 2010;71:14. doi:10.4088/jcp.08r04526gre
- Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. *J Pers Disord*. 2009;23(2):156-174. doi:10.1521/pedi.2009.23.2.156
- Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry*. 2005;162(3):621-624. doi:10.1176/appi.ajp.162.3.621
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245. doi:10.1038/clpt.1981.154
- Andrès E, Villalba NL, Zulfiqar AA, Serraj K, Mourrot-Cottet R, Gottenberg AJ. State of art of idiosyncratic drug-induced neutropenia or agranulocytosis, with a focus on biotherapies. *J Clin Med*. 2019;8(9):1351. doi:10.3390/jcm8091351