

# Valproate-induced Pedal Edema: Troublesome Side Effect yet Neglected?

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## ABSTRACT

Valproate is a commonly used mood stabiliser that has various adverse effects. One such adverse effect is peripheral edema. This case report highlights a case of a 25-year-old female patient who presented with severe pedal edema after starting treatment with valproate for bipolar disorder. The patient had a few other risk factors for edema which makes the diagnosis challenging. Pedal edema is a troublesome adverse effect that can significantly impact the quality of life of patients taking valproate, yet it is often neglected. This case report emphasizes the importance of recognizing and managing valproate-induced peripheral edema in clinical practice.

## Keywords

Sodium valproate; pedal edema; bipolar disorder; mood stabiliser

## INTRODUCTION

Sodium valproate, also known as Epilim, is a mood stabiliser and is indicated for the treatment of acute manic episodes and as maintenance therapy for bipolar disorder in psychiatry<sup>1</sup>. Its extensive use as an adjuvant to antipsychotic in the treatment of psychotic disorder and in the prevention of migraines has been established by the recent expansion of its therapeutic indications<sup>2</sup>.

Like all other medications, it has typical adverse reactions that are frequently observed in daily clinical practise such as tremors and alopecia, but it also causes uncommon adverse reactions that one should be aware of. Peripheral edoema precipitated by sodium valproate is among the unusual ones. It has been noted that taking drugs in high quantities or for an extended period of time may result in this unique side effect<sup>3</sup>.

In this case report, besides taking sodium valproate, the patient also has underlying hepatitis B, which may have contributed to the development of the edema. Moreover,

she was also prescribed with olanzapine, an antipsychotic medication which may also cause peripheral edema<sup>4</sup>. Hence, pinpointing the exact cause of the edema is quite challenging.

## Case study

A 25 year-old lady with underlying Hepatitis B and newly diagnosed Bipolar 1 Disorder was admitted to the psychiatry ward for the first time due to manic symptoms characterised by elated mood, easily irritable, talkativeness, having a lot of ideas and reduced need for sleep for two weeks. She was initially started with tablet sodium valproate 500mg BD in combination with tablet olanzapine 10mg BD. The sodium valproate level was 78.4.

Her mood symptoms subsided with medication after 3 weeks of hospitalization. She was discharged well. However during clinic follow up a month later, she complained of both legs swelling and abdominal distension. Physical examination revealed bilateral pitting pedal edema up to ankle and mild ascites.

First suspicion stemmed from a long-standing hepatitis B problem. Liver enzymes, serum albumin, hepatobiliary system and abdominal ultrasounds, however, did not reveal any anomalies that may have indicated an edema aetiology. Other laboratory investigations

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of complete blood cell count, electrolytes, blood urea nitrogen, serum creatinine, free thyroxine, free triiodothyronine, and thyroid-stimulating hormone, were also within normal limits. Repeated sodium valproate level was 72.9.

Olanzapine dosage was then tapered down to 5mg ON within one month. However, the pedal edema progressed up to mid-shin, disrupting patient's daily activities. Therefore, we switched sodium valproate to lamotrigine 100mg ON while continuing olanzapine 5mg ON.

After two weeks of discontinuing sodium valproate, the pedal edema resolved and patient maintained euthymic with lamotrigine 100mg ON and olanzapine 5mg ON. The score of the Naranjo algorithm, or Adverse Drug Reaction (ADR) Probability Scale, was 5, which corresponded to probable ADR. Later, we managed to off olanzapine and she was maintaining well with monotherapy of lamotrigine 100mg ON.

## DISCUSSION

Pedal edema is one of the dominant signs of a systemic illness such as congestive heart failure, liver and thyroid disease. But it can also be due to local causes such as adverse drug reaction (ADR). Valproate is one of many medications that may cause peripheral edema. Underrecognized and frequently misdiagnosed, valproate-induced peripheral edema typically results in a prescription cascade<sup>6</sup>.

Sodium valproate acts by increasing the amount of gamma-aminobutyric acid (GABA) in the brain through a number of different production and breakdown mechanisms as well as by influencing other neurotransmitters. The medication's usual side effects include tremor, gastrointestinal disturbances, sedation, alopecia, increased hunger, and weight gain<sup>7</sup>. Although the precise mechanism of action is unknown, a speculative explanation for the valproate-related

peripheral oedema could be that the drug specifically enhances GABAergic activity by increasing GABA levels, which affects body fluid dynamics and peripheral vascular resistance and results in a corresponding oedema<sup>7</sup>.

On the basis of earlier findings and our case report, we would like to draw the conclusion that edema brought on by valproate should not be neglected. Because this edema is self-limiting and has no impact on the underlying illness process, clinicians typically disregard the complaint. Even though it is a non-threatening symptom, it can interfere with a patient's everyday activities, causes significant distress in the patient and may lead to treatment non-adherence.

Peripheral edema associated with valproate is a clinically significant side effect which might manifest in days as opposed to years. Early diagnosis and discontinuation of it appears to totally reverse it. Clinicians should therefore be mindful of its potential link to peripheral edema as the therapeutic applications of this medicine are expanded and its subsequent use rises.

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Data gathering and idea owner of this case: Siti Nur Najibah Fauzi

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## References

1. Manning JS. Valproate in bipolar disorder: Case examples from a family practice. *Prim Care Companion J Clin Psychiatry* 1999; **1** (3):71–73.
2. Pagliaro LA and Pagliaro AM. Valproic Acid [Divalproex sodium; Sodium valproate; Valproate sodium]. *PNDR Psychol Neuropsychotropic Drug Ref* 2020; **July**:397–405.
3. Maneerot T, Jenraumjit R, Kijawatpaiboon S and Reungyos J. Low-dose valproate-related peripheral edema in patients with bipolar disorder: Two case reports. *J Clin Psychopharmacol* 2019;**39** (4):412–413.
4. Umar MU and Abdullahi AT. Self-limiting atypical antipsychotics-induced edema: Clinical cases and systematic review. *Indian J Psychol Med* 2016; **38** (3):182–188.
5. Largeau B, Cracowski JL, Lengellé C, Sautenet B and Jonville-Béra AP. Drug-induced peripheral oedema: An aetiology-based review. *Br J Clin Pharmacol* 2021; **87**(8):3043–3055.
6. Ayano G. Bipolar Disorders and valproate: Pharmacokinetics, pharmacodynamics, therapeutic effects and indications of valproate: Review of articles. *Bipolar Disord Open Access* 2016; **02**(02).
7. Lin ST, Chen CS, Yen CF, Tsei JH and Wang SY. Valproate-related peripheral oedema: A manageable but probably neglected condition. *Int J Neuropsychopharmacol* 2009; **12**(7):991–3.