

Comment on: Treatment strategies for clozapine-induced hypotension: A systematic review

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We read with interest the systematic review by Tanzer *et al.*¹ where they summarize 13 case reports and case series of patients with hypotension secondary to clozapine use. The authors should be commended for their efforts in seeking answers for this challenging adverse effect of clozapine. Although recommendations were provided for the management of orthostasis in ambulatory patients in this context, there was minimal attention to patients presenting with profound hypotension and shock secondary to clozapine.

Vasodilatory shock is a form of circulatory failure where there is a global inability to effectively deliver oxygen to tissues and utilize oxygen at the cellular level due to profound arterial vasodilation.² Vasodilatory shock is a medical emergency that warrants prompt intervention to restore arterial blood pressure and reversal of the inciting cause. The syndrome is highly morbid and death rates can be up to 80% depending on the underlying cause.³

In their systematic review, five of the studies identified by Tanzer *et al.* were of patients with refractory shock secondary to maintenance clozapine use or massive ingestion.^{4–8} What is very concerning about these cases that is deserving of more attention is the characteristics of the shock state, specifically the catecholamine vasopressor load that suggests a general lack of response to adrenoceptor agonists (Table 1). Unresponsiveness to high dosages of catecholamine vasopressors has consistently been demonstrated to serve as a poor prognosticator in refractory vasodilatory shock. Specifically, when norepinephrine dosing rates exceed 1 µg/kg/min or 100 µg/min, mortality rates are in excess of 80–90%.^{9,10} Indeed, the cases summarized by Tanzer *et al.* required such high doses of catecholamines (Table 1), and in most cases, necessitated alternative agents for rescue from life-threatening hypotension.

Requirement of high dosages of catecholamines is problematic, because it signals the presence of (a) an uncorrected source that vasopressors cannot fix and (b) prolonged hypotension leading to organ ischemia and multiple organ failure. Further, this excessive adrenoceptor stimulation from escalating dosages increases the opportunity for (c) malignant cardiac arrhythmias, and (d) tissue and organ ischemia.^{2,3} Because clozapine is a potent alpha adrenergic antagonist, saturation of these receptors results in an environment where catecholamines are unable to engage adrenoceptors to produce their vasoconstrictive effects, leaving patients at high risk of experiencing the latter three consequences described above. Therefore, in the case of clozapine ingestion, providing catecholamines and increasing them to toxic dosages without a beneficial hemodynamic effect is not a useful strategy for managing these patients.

To not delay restoration of perfusing pressures, we would caution the use of catecholamines in this setting. Tanzer *et al.* have partially suggested this approach with the avoidance of epinephrine due to paradoxical hypotension (also known as the ‘reverse epinephrine effect’). However, careful observation for an atypical response to norepinephrine is warranted. If an atypical response is noted, immediate application of non-catecholamine vasopressors, such as vasopressin or angiotensin II, should be deployed.

All clinicians should be aware that clozapine is a more potent alpha-antagonist compared with other antipsychotics. The risk of hypotension related to this mechanism is relevant to all fields of medicine, in all levels of care. However, there may be gaps of knowledge as it relates to management of shock secondary to clozapine use. Attention to this issue in the United States may have waned following removal of the *reverse epinephrine effect*

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Table 1. Total vasopressor load reported in studies included in Tanzer *et al.*

	Reported catecholamine dose	Total norepinephrine-equivalent dose
Alagappan <i>et al.</i> ⁴	Norepinephrine 4.3 µg/kg/min Epinephrine 0.19 µg/kg/min	4.49 µg/kg/min
Donnelly and MacLeod ⁵	Dopamine 20 µg/kg/min Epinephrine 0.25 µg/kg/min Norepinephrine 0.25 µg/kg/min	0.7 µg/kg/min
John <i>et al.</i> ⁶	Phenylephrine 1.5 µg/kg/min	0.15 µg/kg/min
Rotella <i>et al.</i> ⁷	Norepinephrine 100 µg/min	1.25 µg/kg/min*
Wieruszewski <i>et al.</i> ⁸	Norepinephrine 1 µg/kg/min Epinephrine 1 µg/kg/min	2 µg/kg/min

*Weight not reported, calculation performed for an 80 kg patient.

from the prescribing information in 2013. Clinicians should continue to report cases of atypical vasopressor responses in the setting of clozapine exposure through regulatory channels in order to better characterize the optimal approach to shock secondary to clozapine use.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Patrick M. Wieruszewski: Conceptualization; Writing – original draft; Writing – review & editing.

Erica D. Wittwer: Writing – review & editing.

Sarah B. Leung: Writing – review & editing.

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Competing interests

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Availability of data and materials

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