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Successful Outpatient Management of Tizanidine Withdrawal Syndrome: A Case Report

Sina Radparvar

Department of Addiction Medicine, Southern California Permanente Medical Group, Sylmar, CA, USA
Email: sina.radparvar@gmail.com

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Abstract

Tizanidine withdrawal syndrome is an infrequently reported condition caused by the abrupt cessation of tizanidine, a short-acting central α_2-adrenergic receptor agonist. This case details a 38-year-old female who presented with moderate withdrawal syndrome induced by the abrupt discontinuation of high-dose tizanidine. The patient presented with autonomic and adrenergic hyperactivity, neuromuscular rebound, and neuropsychiatric disturbances. Management utilized multiple medications targeting hyperadrenergic and autonomic hyperactivity. This was followed by the reintroduction of tizanidine at a lowered baseline dose, which was then gradually reduced using a structured down-taper. The case illustrates an ambulatory detoxification protocol useful for tizanidine withdrawal management.

Keywords

Withdrawal Syndrome, α_2-Adrenergic Agonists, Tizanidine Withdrawal, Tizanidine Dependence, Adrenergic Effect

1. Introduction

Clinically classified as an imidazoline derivative, tizanidine acts as a centrally functioning α_2-adrenergic receptor agonist [1]. This medication was approved by the Food and Drug Administration (FDA) in 1996 for managing muscle spasticity [2]. It is also used off-label to treat headaches, acute lower back and musculoskeletal syndromes [3]. By suppressing presynaptic norepinephrine release from spinal interneurons, tizanidine reduces motor resistance [4]. However, this mechanism also decreases blood pressure and heart rate [2]. While abrupt cessation is

known to precipitate withdrawal, there is currently a significant knowledge gap regarding established, standardized ambulatory protocols for managing high-dose dependence in the outpatient setting.

Chronic use of Tizanidine, especially at high doses and long duration, can induce the downregulation and internalization of α_2-adrenergic receptors, leading to physical dependence and rebound syndrome [3] [5]. Sudden drug discontinuation can cause a massive catecholamine surge in the central nervous system due to the loss of functional presynaptic α_2-receptors [6]. This withdrawal manifests as a complex clinical spectrum of autonomic and adrenergic hyperactivity, neuromuscular rebound, and neuropsychiatric disturbances [3] [6]-[8].

The presentation of tizanidine withdrawal varies widely based on baseline dosage, therapy duration, patient clearance rates, and drug-drug interactions. Case reports in the literature demonstrate a broad spectrum of tizanidine withdrawal presentations [1] [2] [4] [6]-[9]. Clinical manifestations range from mild muscle tightness and anxiety to moderate presentation such as rebound hypertension, reflex tachycardia, diaphoresis, chills, low-grade fever, and gastrointestinal distress. In severe cases, patients may experience life-threatening hypertensive crises, hyperthermia, severe hypertonicity, and delirium.

The present study highlights a successful strategy for outpatient management of moderate tizanidine withdrawal syndrome. This case report describes a 38-year-old female with a high dose tizanidine dependency who experienced acute hyperadrenergic autonomic instability, rebound spasticity, and severe neuropsychiatric distress following abrupt drug cessation. The patient met the criteria for a substance use disorder, presenting with significant functional impairment across social and occupational domains. An ambulatory treatment strategy is outlined using multisystem stabilization medications followed by a structured tizanidine reinstatement and gradual taper, offering a variable clinical pathway for outpatient receptor clearance and symptom mitigation.

2. Case Presentation

2.1. History of Present Illness

A 38-year-old female presented to the Addiction Medicine clinic as an urgent walk-in with a 24-hour history of chest discomfort, palpitations, diaphoresis, severe, persistent nausea, headache, generalized anxiety, agitation, uncontrollable racing thoughts, and insomnia. She also noted worsening generalized muscle stiffness, fine hand tremors, and physical restlessness. The patient had a history of chronic myofascial pain syndrome and lumbar radiculopathy. Her daily home regimen consisted of Ibuprofen 400 mg four times a day and tizanidine 32 mg, taken in four divided 8 mg doses. However, for the last 18 months, the patient escalated dosage of tizanidine to 64 mg per day. She reported seeking the medication's calming and sedating effects from the "black market" or non-prescribed sources to manage persistent pain symptoms. Over an 18-month period, her escalation to illicit tizanidine resulted in severe social isolation, marital conflict, and

the loss of long-term employment. Due to an unanticipated disruption in her illicit drug supply, she abruptly ran out of her medication 24 hours prior to presentation. She was not taking any other daily medications.

2.2. Social History, Psychiatric History & Family History

Social history was negative for tobacco use, nicotine vaping, alcohol consumption, or recreational drug history (including cannabis, stimulants, or illicit synthetic substances). She had no personal history of substance use disorder, previous addiction history, or prior withdrawal episodes involving prescribed or over-the-counter medications. Her psychiatric history was remarkable only for generalized anxiety disorder, with no prior psychiatric hospitalizations or high-risk behaviors. Family history was completely negative for substance use disorders, major psychiatric illnesses, or premature cardiovascular disease. Furthermore, a review of her medication history revealed no recent use of CYP1A2-interacting drugs or herbal supplements (such as ciprofloxacin, fluvoxamine, or acyclovir) that could have altered tizanidine metabolism or clearance prior to the acute cessation event. The patient had a 12-year history of stable, high-level employment in corporate human resources. Since her tizanidine use intensified in the last 18 months, her functioning deteriorated as she experienced "brain fog", slow processing speeds and erratic emotional outbursts during the workday. She frequently missed morning meetings due to severe early-morning withdrawal symptoms (nausea, tremors, intense anxiety). Following several department audits, her employment was terminated two months before clinic visit. The patient also reported concealing illicit drug purchases from her spouse. The financial strain of spending over $300 per week on illicit medications, combined with emotional withdrawal and deception, led to separation from her spouse and social isolation.

2.3. Physical Examination

At presentation, the patient's body mass index (BMI) was 23.4 mg/m^2, falling within the normal weight range. The patient appeared anxious, restless, and in mild acute distress during the examination. The clinical evaluation revealed significant autonomic and neuromuscular abnormalities, the details of which are comprehensively achieved in Table 1.

2.4. Diagnostic Tests

The diagnostic workup for the patient's suspected tizanidine withdrawal focused on assessing hyperadrenergic state and evaluating cardiac, pulmonary, gastrointestinal, hepatic, renal and neuropsychiatric end-organ function. Furthermore, the diagnostic evaluation sought to exclude infectious processes, rhabdomyolysis, hepatotoxicity, and confounding substance toxicities. Table 2 details the laboratory and diagnostic workup, including specific finding values and their pathophysiological significance for this case.

Table 1. Vital signs and physical examination components matrix.

System	Clinical Component	Observed Findings
General	Appearance	Visibly distressed, guarding, and rocking in her chair with marked psychomotor agitation. Alert and oriented.
Vital Signs	Blood Pressure	170/110 mm Hg
	Heart Rate	110 bpm (reflex tachycardia)
	Temperature	99.2˚F (37.3˚C)
	Respiratory Rate	22 breaths per minute (tachypnea)
Skin	Integumentary	Profuse diaphoresis and generalized flushing.
Cardiovascular	Precordium	Hyperdynamic precordium with regular, rapid rhythm; loud S1 and S2 sounds.
	Peripheral Vascular	Delayed capillary refill (>2 seconds).
Gastrointestinal	Abdomen	Diffuse, mild tenderness to palpation secondary to severe, constant nausea and retching.
	Bowel Motility	Hyperactive bowel sounds.
Neuromuscular	Muscle Tone	Rebound hypertonia and severe generalized rigidity.
	Tremor	High-frequency, low-amplitude fine postural tremor in upper extremities upon extension.
	Reflexes	Diffuse hyperreflexia (3+ to 4+ deep tendon reflexes) with sustained clonus.
Psychiatric	Behavior	Frequent pacing of the examination room.
	Cognitive/Speech	Hypervigilance, racing speech, and unprovoked racing thoughts impairing sustained attention.
	Affect/Mood	Generalized anxiety with an expressed sense of impending doom.

Abbreviations: bpm, beats per minute; mm Hg, millimeters of mercury; S1/S2, first and second heart sounds.

Table 2. Diagnostic tests & laboratory workup.

Diagnostic Test	Finding/Value	Normal Reference Range	Clinical Rationale & Significance
12-Lead ECG	Sinus tachycardia at 115 bpm	N/A	Tachycardia due to sympathetic over activity
Cardiac Biomarkers	Troponin I (Serial): Negative < 0.01 ng/ml (at presentation & 6 hours)	<0.03 ng/ml	Ruled out acute myocardial injury or infarction as the cause of her chest discomfort.
Respiratory & Oxygenation Monitoring	Pulse Oximetry at 96%	≥95% on room air	Indicated adequate oxygenation despite tachypnea and severe anxiety.

Continued

Hematological Profile	WBC: 6.4 × 10^3/μL Hgb: 13.8 g/dL Plt: 245 × 10^3/μL	4.5 - 11.0 × 10^3/μL 12.0 - 15.5 g/dL 150 - 450 × 10^3/μL	Excludes underlying infectious processes, leukocytosis from severe acute stress, or occult anemia contributing to tachycardia
Metabolic & Renal Profile	Potassium: 4.0 mEq/L Sodium: 147 mEq/dL BUN: 25 mg/dL Creatinine: 0.78 mg/dL Lactic Acid: 1.1 mmol/L	3.5 - 5.0 mEq/L 135 - 145 mEq/dL 7 - 20 mg/dL 0.5 - 1.2 mg/dL 0.5 - 2.2 mmol/L	Mild hypernatremia and prerenal azotemia indicated dehydration due to volume depletion and free-water loss. Normal lactic acid ruled out systemic tissue hypoperfusion or metabolic crisis.
Liver Function Tests	ALT: 115 U/L AST: 92 U/L ALP: 88 U/L Total Bilirubin: 0.9 mg/dL	7 - 56 U/L 10 - 40 U/L 44 - 147 U/L 0.1 - 1.2 mg/dL	Indicated mild, transient tizanidine-induced hepatotoxicity.
Skeletal Muscle Biomarkers	CK: Baseline (Day 1): 942 U/L Repeat (Day 5): 185 U/L	Female: 26 - 192 U/L	Confirmed early skeletal muscle breakdown from rigidity; repeat testing proved resolution and ruled out progressing rhabdomyolysis.
Endocrine/Thyroid Studies	TSH: 1.85 mIU/L Free T4: 1.2 ng/dL	0.4 - 4.0 mlUI/L T4: 0.8 - 1.8 ng/dL	Excluded an underlying thyrotoxic crisis or hyperthyroidism as source for her hyperadrenergic state.
Urine Toxicology Screen	Negative	Negative	Excluded confounding toxicities, acute illicit drug use, or alternative alcohol or drug withdrawal states.
Reproductive Health	Serum β-hCG: Negative	N/A	Performed as a mandatory safety screen for a female of childbearing age before initiating a high-risk multi-drug taper

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; ECG, electrocardiogram; Free T4, free thyroxine; Hgb, hemoglobin; N/A, not applicable; Plt, platelets; β-hCG, beta-human chorionic gonadotropin; TSH, thyroid-stimulating hormone; WBC, white blood cells.

2.5. Differential Diagnosis

Given the patient's autonomic hyperactivity, neuromuscular irritability, and severe anxiety, a broad differential diagnosis was evaluated to rule out life-threatening conditions and confounding toxicological etiologies.

Sepsis and Systemic Infection: Fever (99.2˚F), Tachycardia (110 bpm), tachypnea (22 breaths/min), and diaphoresis initially raised suspicion for early systemic inflammatory response syndrome (SIRS). However sepsis was rapidly excluded due to the complete absence of a localized infectious source, a normal lactate level, and a hemodynamic profile that stabilized without fluid resuscitation or vasoactive support.

Thyrotoxic Crisis (Thyroid Storm): Acute thyrotoxicosis can cause profound hyperthermia, severe cardiovascular instability (including tachycardia, hypertension, and arrhythmias), and psychomotor agitation. This endocrine emergency was confidently ruled out by a normal thyroid-stimulating hormone (TSH) level of 1.85 mIU/L and a free thyroxine (Free T4) level of 1.2 ng/dL, coupled with the absence of an enlarged thyroid gland, exophthalmos, or a history of goiter.

Substance Withdrawal Syndromes: Severe alcohol withdrawal (delirium tremens) and sedative-hypnotic discontinuation closely mimic severe α_2-agonist withdrawal. These were definitively ruled out by a comprehensive urine toxicology screen that was completely negative, the absence of alcohol metabolites, and a reliable, collateral history confirming no ethanol or sedative misuse.

Stimulant Intoxication: Acute intoxication from cocaine, amphetamines, or synthetic cathinones was a strong initial consideration. However, the patient's symptoms completely aligned with a known 24-hour tizanidine cessation window, her pupils were normal (not mydriatic), and the urine drug screen was negative for all major illicit stimulants.

Serotonin Syndrome: Features of neuromuscular hyperactivity (rigidity, hyperreflexia), autonomic instability, and severe agitation strongly overlapped with serotonin toxicity. However, the patient lacked any exposure to serotonergic agents. Furthermore, she completely lacked the classic ocular clonus or prominent gastrointestinal symptoms characteristically required to fulfill the Hunter Criteria for diagnosis.

Pheochromocytoma: This catecholamine-secreting tumor was considered due to episodic hypertension, tachycardia, and diaphoresis. It was ruled out by the patient's immediate, durable clinical response to tizanidine reinstatement and the absence of prior paroxysmal hypertensive crises.

Acute panic attack: While acute panic attacks cause paroxysmal hypertension and chest tightness, a primary psychiatric etiology could not account for her objective neuromuscular signs, including generalized rigidity, high-amplitude postural tremors, and an elevated creatine kinase (942 U/L).

2.6. Diagnostic Assessment

No objective biomarker exists for α_2-agonist withdrawal. Therefore, the diagnosis of moderate tizanidine withdrawal syndrome was established based on clinical history and presentation. Specifically, the symptoms began immediately after abrupt tizanidine cessation, mirrored classic hyperadrenergic and neuromuscular pathways, and rapidly resolved upon tizanidine reintroduction. The exclusion of all major infectious, endocrine, toxicological, and psychiatric mimics further confirmed the diagnosis. Evaluation of the patient's tizanidine use confirmed a problematic pattern leading to clinically significant impairment. The patient met 11 of the 11 DSM-5-TR criteria [10], supporting a diagnosis of a severe substance use disorder. These criteria are shown in **Table 3**.

Table 3. DSM-5 substance use disorder criteria mapping for high-dose tizanidine dependence.

DSM-5 Diagnostic Domain	Specific Diagnostic Criterion	Observed Clinical Presentation & Evidence
Impaired Control	1. Larger Amounts/Long Duration	Met. Patient escalated non-prescribed tizanidine use over an 18-month period, ultimately reaching an exceptionally high dose of 64 mg per day.
	2. Unsuccessful De sires to Cut Down	Met. Patient made multiple unsuccessful attempts to manage worsening chronic pain and persistent withdrawal symptoms independently.
	3. Excessive Time Spent	Met. Significant time was dedicated to illicitly sourcing tizanidine from non-prescribed "black market" avenues once her legal drug supply was disrupted.
	4. Cravings or Intense Urges	Met. Experienced intense daily cravings and an escalating pattern of frequent re-dosing driven by the rapid drop in tizanidine plasma concentrations.
Social Impairment	5. Failure to Fulfill Role Obligations	Met. Suffered a severe decline in occupational performance due to early-morning withdrawal symptoms and cognitive impairment, culminating in job termination.
	6. Interpersonal & Social Problems	Met. Sustained ongoing non-prescribed use despite experiencing profound marital conflict and severe social isolation.
	7. Activities Given Up or Reduced	Met. Progressively withdrew from family interactions, missed critical morning work meetings, and abandoned social circles over a 12-month period.
Risky Use	8. Use in Physically Hazardous Situations	Met. Continued to ingest unverified, illicitly sourced medication from non-prescribed channels, introducing significant chemical and contamination safety risks.
	9. Use Despite Physical/Psych Problems	Met. Continued escalating her dosage despite experiencing objective adverse consequences, including profound morning withdrawal anxiety, tremors, and "brain fog."
Pharmacological	10. Physiological Tolerance	Met. Demonstrated marked physiological tolerance, requiring a continuous escalation of her daily dose up to 64 mg to achieve the initial calming and sedative effects.
	11. Withdrawal Syndrome	Met. Developed a moderate, multi-system hyperadrenergic crisis consisting of rebound hypertension (170/110 mm Hg), tachycardia, tremors, and elevated CK levels within 24 hours of abrupt cessation.

Note. Adapted from *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., text rev., p. 653), by the American Psychiatric Association, 2022 [10].

2.7. Treatment Approach

The acute management of tizanidine withdrawal focused on immediate hemodynamic stabilization and the mitigation of central autonomic hyperarousal. Hemo-

dynamic stabilization was achieved using clonidine (a central α_2 agonist) and labetalol (a combined α_1, β_1, and β_2 antagonist). Labetalol was used as a secondary agent to further reduce blood pressure via α_1-mediated vasodilation while concurrently blocking β-adrenergic pathways.

To manage central autonomic hyperarousal and anxiety symptoms, lorazepam (positive allosteric modulator of the GABA-A receptor) was administered to enhance inhibitory neurotransmission and rapidly halt the hyperadrenergic state, tachycardia, and severe psychological agitation.

Nausea and vomiting were initially managed with sublingual ondansetron (a 5-HT_3 receptor antagonist). Following an inadequate clinical response, therapy was escalated to rectal prochlorperazine (a D_2-dopamine receptor antagonist) to achieve optimal antiemetic control and bypass the upper gastrointestinal tract.

To address hyperthermia and breakthrough musculoskeletal pain, acetaminophen was utilized for its central actions on the hypothalamic heat-regulating center and its systemic analgesic effects.

Following acute stabilization, tizanidine was reintroduced at lower doses. A structured, multi-week down-titration of tizanidine was subsequently implemented alongside targeted supportive therapies to facilitate safe receptor up-regulation. During this phase, persistent sleep and appetite disturbances were treated with bedtime mirtazapine. This medication was initiated on day 6 after tapering off lorazepam, leveraging its potent central H_1-receptor antagonism to mitigate withdrawal-induced insomnia and anorexia. The patient tolerated the process but complained of symptoms of body aches, insomnia, poor appetite and anxiety during this phase.

Comprehensive details regarding the specific pharmaceutical interventions, dosing regimens, and underlying pathophysiological rationales across each treatment phase are outlined in **Table 4**.

Table 4. Clinical protocol used in the case report for management of tizanidine withdrawal syndrome.

Phase and Timeline	Medication	Dosage and Route	Clinical Rationale
Acute Clinic Phase (*Day* 1)	Ondansetron	4 mg sublingually (initial first-line dose)	First-line antiemetic to control severe nausea and vomiting.
	Prochlorperazine	25 mg rectally (alternative dose)	Second-line alternative therapy for refractory emesis.
	Clonidine	0.1 mg orally (single dose)	Rapidly suppresses hyper adrenergic withdrawal symptoms.
	Labetalol	100 mg orally (single dose; titrate as needed)	Provides dual α/β blockade fir immediate blood pressure and heart rate control.
	Lorazepam	1 mg orally (single dose)	Dampens profound anxiety, racing thoughts, and physical agitation.

Continued

Taper Phase (*Days* 2 - 21)	Tizanidine Reintroduction (*Days* 2 - 7)	8 mg orally four times daily (32 *mg/day total*)	Re-establishes α-2-receptor binding to completely suppress withdrawal. *Note: Oral clonidine discontinued to prevent toxicities.*
	Tizanidine Step-Down 1 (*Days* 8 - 14)	8 mg orally three times daily (24 *mg/day total*)	Initiates gradual dose reduction to allow safe receptor up-regulation.
	Tizanidine Step-Down 2 (*Days* 15 - 21)	4 mg orally three times daily (12 *mg/day total*)	Final weaning tier to minimize the risk of rebound symptoms before full discontinuation.
Supportive Phase (*Concurrent with Taper*)	Lorazepam (*Days* 1 - 5)	0.5 mg orally every 8 hours as needed	Short-term breakthrough control for anxiety and acute agitation; discontinued early to prevent dependence.
	Mirtazapine (*Days* 6 - 21)	7.5 - 15 mg orally at bedtime	Manages withdrawal-induced insomnia, poor appetite, and underlying anxiety.
	Ondansetron (*Days* 1 - 21)	4 - 8 mg orally or sublingually every 8 hours as needed	First-line suppressive therapy for nausea.
	Prochlorperazine (*Days* 1 - 21)	5 - 10 mg orally or 25 mg rectally every 6 hours as needed	Second-line antiemetic for persistent or breakthrough emesis.
	Acetaminophen (*As Needed*) (*Days* 1 - 21)	325 - 500 mg orally or rectally every 4 - 6 hours as needed	Manages body aches, muscular pain, and low-grade fever.

2.8. Clinical Course and Timeline

To mitigate social isolation and environmental stressors, the patient agreed to reside with her mother as a care partner for ongoing clinical monitoring during the treatment phase. The patient's acute withdrawal syndrome resolved along a distinct, sequential timeline. Initial clinical improvement emerged within two hours of administering our urgent stabilization protocol—consisting of clonidine, labetalol, lorazepam, and sublingual ondansetron—at the walk-in clinic. Before discharge, her objective hyperadrenergic signs, most notably severe diaphoresis, visible tremors, and acute psychomotor agitation, had noticeably diminished. To address the residual neuromuscular rebound, we restarted scheduled tizanidine on Day 2 at 8 mg four times daily. Following reinstatement, the patient's rebound hypertension and tachycardia resolved completely within 24 to 36 hours, stabilizing to a baseline of 122/74 mmHg and a heart rate of 72 beats per minute by the end of Day 3. Severe nausea and gastrointestinal distress abated by Day 4, enabling her care partner to transition from rectal rescue antiemetics to oral supportive medications. Although withdrawal-induced insomnia and profound anxiety proved more stubborn, both showed significant, steady improvement by Day 8 following the introduction and upward titration of bedtime mirtazapine on Day 6. This step-

by-step stabilization ultimately maintained patient safety and comfort, ensuring strict adherence throughout the subsequent taper phases.

2.9. Outcome and Follow-Up Laboratory Trends

A repeat liver function panel was checked on Day 10 (mid-taper) and Day 28 (one week after complete tizanidine discontinuation) and is listed below:

Initial Presentation (Peak Exposure): ALT 115 U/L|AST 92 U/L (Normal: ALT 7 - 56 U/L; AST 10 - 40 U/L).

Day 10 (Mid-Taper De-escalation): ALT 78 U/L|AST 55 U/L.

Day 28 (Post-Discontinuation Follow-Up): ALT 38 U/L|AST 28 U/L (Full Resolution).

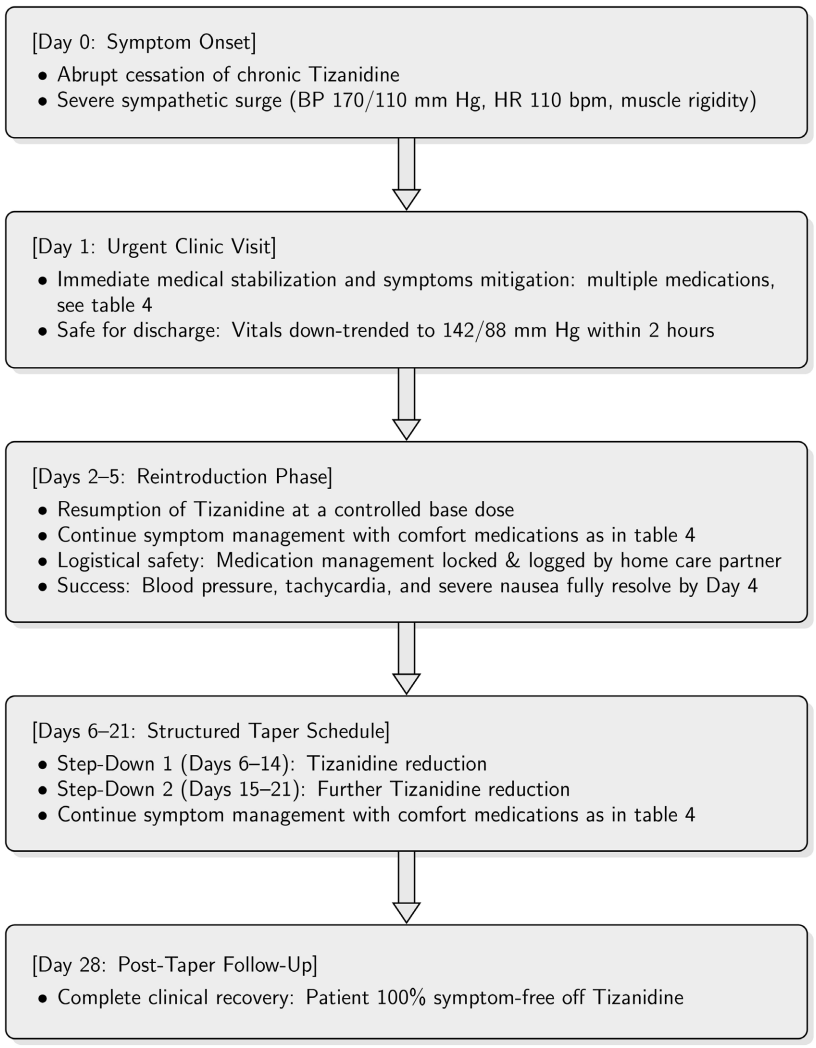

Figure 1. Chronological Treatment Timeline and Clinical Course. Schematic mapping the patient's progression from high-dose tizanidine cessation (Day 0) through urgent ambulatory stabilization (Day 1) and partner-supervised reintroduction (Days 2 - 5). The subsequent structured step-down tapering protocol, inclusive of adjunctive medications (Days 6 - 21), and final objective symptom and laboratory normalization at the 28-day exit assessment are delineated.

At the four-week clinical follow-up, the patient demonstrated complete resolution of the withdrawal syndrome alongside normalization of hepatic transaminases. Her gastrointestinal as well as neuro psychiatric symptoms had entirely subsided, and her blood pressure remained stable at 122/74 mmHg. Additionally, both sleep architecture and appetite had returned to baseline. The patient's complete chronological progression and multi-phase outpatient treatment timeline are visually summarized in Figure 1.

3. Discussion

3.1. Pathophysiological Mechanisms of Withdrawal

Tizanidine abuse remains uncommon due to the high doses required to reach intoxication that can cause uncomfortable side effects such as dry mouth, muscle weakness, severe drowsiness, dizziness, and low blood pressure [11]. Because it lacks euphoric effects, tizanidine is not classified as a controlled substance in the Unites States and is generally viewed as having a lower addiction liability than opioids and benzodiazepines.

Large-scale epidemiologic data tracking tizanidine use disorder is limited. However, several case studies in the literature document the potential for tizanidine dependence and withdrawal syndrome [1] [4] [6]-[9] [12] [13]. The medication's specific pharmacologic properties place certain individuals at risk for abuse and physical dependence.

This case report details an unusual presentation of tizanidine dependence complicated by withdrawal syndrome. Tizanidine exerts its effect via central α_2-adrenergic receptor activation, reducing sympathetic outflow. Abrupt cessation in a dependent person can cause severe hyper-adrenergic autonomic instability with cardiovascular, autonomic, neuromuscular and psychiatric symptoms as seen in this case report.

Figure 2 illustrates the proposed pathophysiology of the withdrawal syndrome based on the patient's clinical presentation in this case report.

Tizanidine undergoes extensive hepatic first-pass metabolism (40% - 95%) and features a brief 2.5-hour half-life [1]. Consequently, plasma concentrations drop rapidly post-ingestion, which can prompt frequent re-dosing patterns and subsequent misuse. This first-pass metabolism is mediated via the highly polymorphic cytochrome P450 1A2 (CYP1A2) pathway, driving substantial inter-individual genetic variability in drug clearance and systemic exposure [2]. Such enzymatic variance renders dependency less predictable, altering addiction risks and exacerbating withdrawal severity in rapid metabolizers [14]. In selected individuals, accelerated clearance causes plasma concentrations to drop precipitously upon cessation. This rapid systemic evacuation prevents central nervous system receptors from executing gradual homeostatic adjustments, culminating in abrupt receptor uncoupling that can trigger a severe, accelerated withdrawal syndrome [14]. Although pharmacogenetic testing was unavailable in this case to confirm the patient's specific CYP1A2 genotype or identify subclinical drug-supplement inter-

actions, individual enzymatic variability remains a compelling mechanistic hypothesis to explain the rapid onset and severity of her withdrawal.

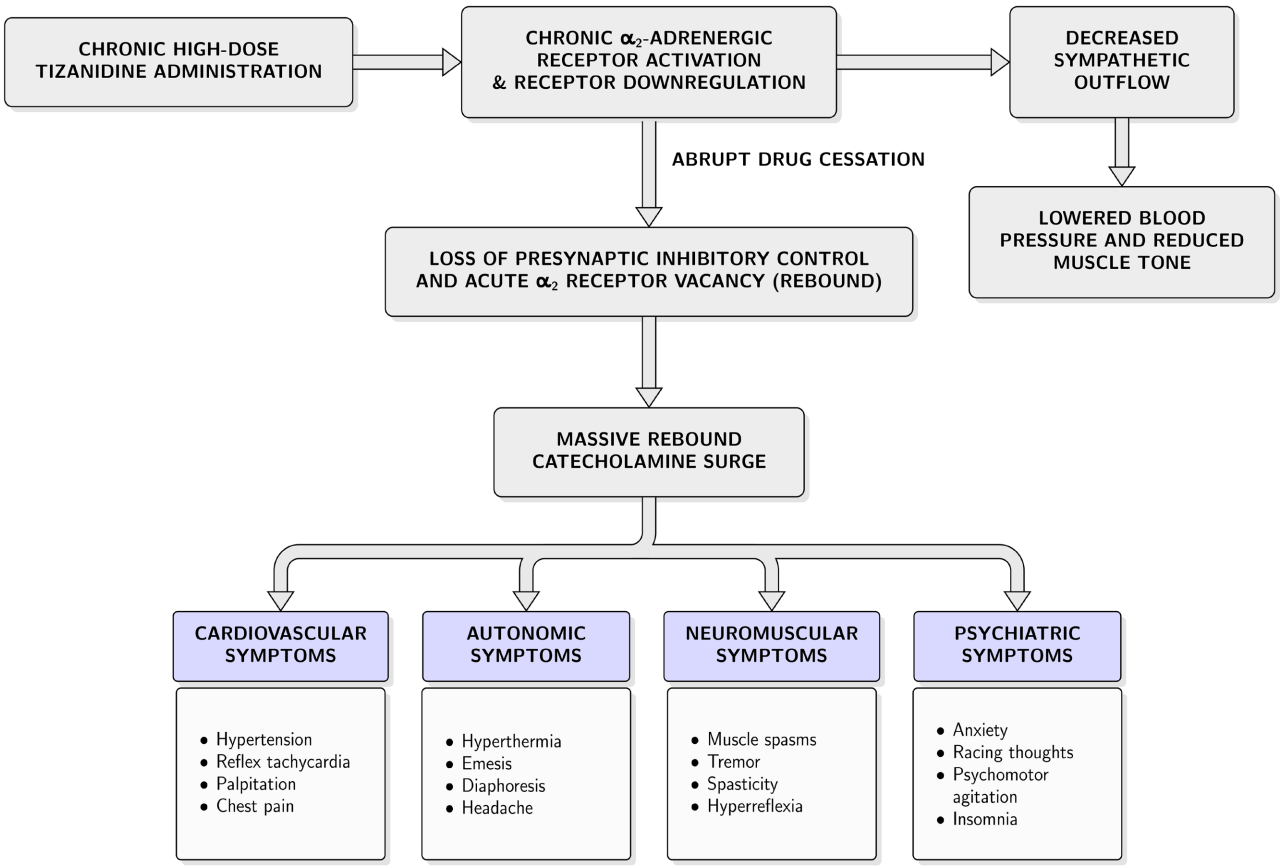

Figure 2. Hypothesized pathophysiological mechanism of high-dose tizanidine withdrawal. Conceptual model illustrating central α_2-adrenergic receptor downregulation during chronic exposure and the subsequent hyperadrenergic surge upon abrupt cessation. This schematic represents a generalized, evidence-informed mechanism derived from established α_2-agonist literature rather than patient-specific experimental data.

3.2. Diagnostic Evaluation

The diagnostic evaluation for suspected tizanidine withdrawal aims to identify the severity of symptoms such as hyperadrenergic states as well as any end-organ impairment. Additionally, the assessment should exclude infectious processes, rhabdomyolysis, hepatotoxicity, sepsis, thyrotoxicosis, and confounding substance toxicities. Review of severe cases in the literature indicates that abrupt tizanidine cessation can induce a massive catecholamine surge, leading to profound hyperadrenergic symptoms, hypertensive crisis, or severe neuropsychiatric distress that requires emergency department evaluation and hospitalization [4] [8]. In this case report, however, the clinical presentation was characterized by moderate symptoms and mild end-organ involvement; thus, outpatient treatment was deemed reasonable.

Because validated scoring tools—such as COWS (Clinical Opiate Withdrawal Scale) or CIWA-Ar (Clinical Institute Withdrawal Assessment of Alcohol Scale,

Revised)—do not exist for centrally acting α_2-adrenergic agonist withdrawal, we classified this case as "moderate" by evaluating three clinical dimensions: autonomic hyperactivity, neuromuscular rebound, and end-organ strain. While mild withdrawal typically manifests as localized muscle tightness, baseline anxiety, and negligible hemodynamic shifts, severe or malignant withdrawal involves life-threatening autonomic storms, malignant hyperthermia, rigid hypertonicity requiring muscle paralysis, acute coronary syndrome, or delirium and psychosis. The patient's presentation sat between these two extremes. Her objective findings transcended a mild classification, marked by symptomatic rebound hypertension (170/110 mm Hg), reflex tachycardia (110 bpm), generalized rigidity, high-amplitude postural tremors, and transient laboratory derangements, including hepatotoxicity (ALT 115 U/L) and skeletal muscle breakdown (CK 942 U/L). However, she lacked the defining features of malignant withdrawal. Crucially, the patient remained alert, oriented, and cooperative, with no neuropsychiatric decompensation. Furthermore, her chest discomfort was devoid of ischemic ECG changes, and her vital organ systems remained compensated without progressing to hypertensive encephalopathy, overt rhabdomyolysis, or hyperthermia. This constellation of multi-system objective symptoms, in the absence of life-threatening end-organ failure or delirium, established the clinical basis for a moderate designation.

3.3. Outpatient Treatment Strategy and Safety Infrastructure

Designing a treatment plan for tizanidine withdrawal requires balancing immediate cardiovascular stability with long-term neuroreceptor recovery. For this patient, we built a flexible, three-phase outpatient strategy: initial multi-system stabilization, a careful reintroduction and cross-tapering phase, and long-term adjunctive symptom management. While the existing literature offers several inpatient interventions such as clonidine, β-blockers, phenobarbital, or dexmedetomidine [4] [6] [8] [9] [12] [13], clinicians currently lack any standardized guidelines for managing high-dose dependence safely at home.

Choosing an outpatient pathway meant weighing the patient's strong preference against the obvious clinical risks. Ultimately, we felt outpatient care was justified because the patient had an excellent track record of treatment adherence, a reliable 24-hour caregiver at home, and showed immediate hemodynamic improvement during her initial two-hour clinic evaluation. To safely replicate the protective boundaries of an inpatient ward, we put a strict home-safety infrastructure in place:

At-Home Care Supervision: A dedicated care partner (patient's mother) took full control of storing, tracking, and giving all scheduled medications. Keeping everything in a locked container prevented any accidental double-dosing or oversedation, and the care partner was thoroughly trained to spot emerging red-flag symptoms.

Rigorous Home Monitoring: Vitals (blood pressure, heart rate, and temperature) were checked three times a day. It was crucial that these were logged right

before giving any rescue or as-needed medications to avoid causing severe hypotension or compounding sedation.

High-Frequency Clinical Follow-Up: Our clinical team conducted daily telehealth visits during the acute stabilization phase (Days 1 - 5) to visually check the patient's neuromuscular tone, evaluate her anxiety, and ensure compliance. We then transitioned to twice-weekly in-person visits during the tapering phase (Days 6 - 21) to evaluate deep tendon reflexes and monitor her resolving transaminases.

Explicit Emergency Thresholds: We gave the family written instructions to return immediately to the emergency department if the patient crossed specific objective boundaries. These included a systolic BP over 160 mm Hg, a diastolic BP over 100 mm Hg, or a heart rate over 110 bpm on two consecutive readings taken 15 minutes apart despite using rescue medications. We also instructed them to seek immediate care for acute confusion, hallucinations, worsening chest pain, or a fever over 101.5˚F.

3.4. Case Study Limitations

A primary limitation of this case study is our simultaneous use of a multi-drug regimen during acute stabilization, which prevents us from isolating the exact therapeutic contribution of each individual medication. Because we administered clonidine, labetalol, lorazepam, and tizanidine concurrently or in rapid succession, their pharmacodynamic effects inevitably overlapped. While this combined approach introduces confounding variables, we chose it intentionally based on a multi-system therapeutic rationale. Single-agent therapy would not have sufficed to manage the patient's broad spectrum of autonomic, neuromuscular, and neuropsychiatric distress. Concurrent administration allowed our clinical team to safely target distinct physiological pathways at the same time. Future comparative trials must determine if a more streamlined, single-agent protocol can achieve similar ambulatory success.

Reviewing the sparse literature on tizanidine withdrawal underscores the unique clinical profile and therapeutic strategy of this case. Previously reported cases consistently describe severe withdrawal syndromes mandating intensive care or inpatient admission due to life-threatening complications, including malignant hyperthermia, rigid hypertonicity requiring active muscle paralysis, rhabdomyolysis, or delirium and acute psychosis [4] [8]. While our patient shared key clinical features with these reports—namely, a severe sympathetic storm within 24 hours of cessation, marked rebound hypertension, and reflex tachycardia—she differed significantly by maintaining full neurocognitive clarity and exhibiting no end-organ damage. Three distinct factors drove the success of our ambulatory protocol, where historical cases required prolonged hospitalization:

Early, Targeted Intervention: Evaluating and treating the patient early in her withdrawal trajectory allowed us to administer clonidine and labetalol concurrently. This arrested the catecholamine surge before it could escalate into a hypertensive crisis or encephalopathy.

Pathophysiological Reversal: Rather than relying solely on high-dose sedative-hypnotic infusions to manage agitation, our strategy addressed the root cause of the syndrome. We rapidly reinstated tizanidine to reoccupy down-regulated receptors, followed by a gradual taper.

A Rigorous Psychosocial Safety Net: While published cases often involved unmanaged polysubstance use or isolated social environments, our patient had a reliable, 24-hour home care partner. This partner secured medications, monitored vital signs three times daily, and followed strict emergency thresholds. This case demonstrates that when neurocognitive clarity is preserved and a robust home-monitoring framework is present, early targeted receptor reintroduction can safely bypass expensive inpatient admissions.

This case report illustrates that carefully selected patients with moderate tizanidine withdrawal may be successfully managed in the outpatient setting using a structured taper and close clinical follow-up. Larger studies are needed before this approach can be recommended more broadly.

Declarations

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and associated clinical data. A copy of the executed consent document is available for inspection by the Editor-in-Chief upon request.

Ethical Approval: Institutional Review Board (IRB) review and formal ethics approval were waived by the institutional research ethics committee. This waiver was granted on the grounds that the manuscript constitutes a retrospective single-case report of standard clinical care and contains no personally identifiable patient information.

Artificial Intelligence (AI) and Language Assistance Disclosure:

Grammarly (an AI-assisted editing tool) was utilized during the preparation of this manuscript solely to improve language quality, refine English grammar, and enhance readability. The authors retain full responsibility for the accuracy, originality, and scientific conclusions of the work.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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