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(RESEARCH ARTICLE)

The hidden cost of comfort: A case series on amitriptyline's multisystem adverse effects

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Abstract

Background: Amitriptyline, a tricyclic antidepressant (TCA), is widely prescribed for chronic pain, insomnia, and mood disorders. Despite its efficacy, its anticholinergic and neurological adverse drug reactions (ADRs) are often underrecognized, particularly in elderly patients or those with multiple comorbidities.

Objective: To describe six clinically significant adverse reactions associated with amitriptyline through detailed case reports from a tertiary care center.

Methods: Case reports were compiled from an Adverse Drug Reaction Monitoring Centre using standardized causality, severity, and preventability assessment scales.

Results: Six patients (aged 23–77) developed ADRs, including dry mouth, constipation, somnolence, obstructive voiding, vertigo, akathisia, and manic symptoms. All ADRs were classified as "Type A" and "Probable" by WHO-UMC criteria, with most deemed "Probably Preventable" based on the Schumock and Thornton scale.

Conclusion: Amitriptyline's adverse effects are not dose-limited and may occur even at low doses. Regular monitoring, patient-specific dosing, and pharmacovigilance are essential for minimizing risks.

Keywords: Amitriptyline; Adverse Drug Reactions; Anticholinergic; Elderly; Pharmacovigilance; Case Series

1. Introduction

Amitriptyline is a tricyclic antidepressant (TCA) primarily approved for the treatment of major depressive disorder but widely prescribed for off-label indications such as neuropathic pain, fibromyalgia, migraine prophylaxis, and insomnia due to its analgesic and sedative properties [1,2]. It acts by inhibiting the reuptake of serotonin and norepinephrine in the central nervous system, thereby enhancing mood and pain modulation. However, its pharmacodynamic profile includes strong anticholinergic, antihistaminic, and alpha-adrenergic blocking effects, which significantly increase the risk of adverse drug reactions (ADRs), especially in vulnerable populations like the elderly or those with multiple comorbidities [1,3,5].

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While commonly reported side effects include dry mouth, sedation, constipation, and blurred vision, more serious but underrecognized ADRs such as urinary retention, akathisia, vertigo, and manic episodes can occur even at low doses [4,6]. These adverse reactions may mimic underlying disease progression or age-related decline, leading to misdiagnosis or delayed management. Moreover, pharmacogenetic variability, drug-drug interactions, and altered metabolism in aging populations compound the risks. This case series presents a real-world overview of such adverse effects, highlighting the urgent need for routine monitoring, personalized prescribing, and heightened clinical vigilance when using amitriptyline.

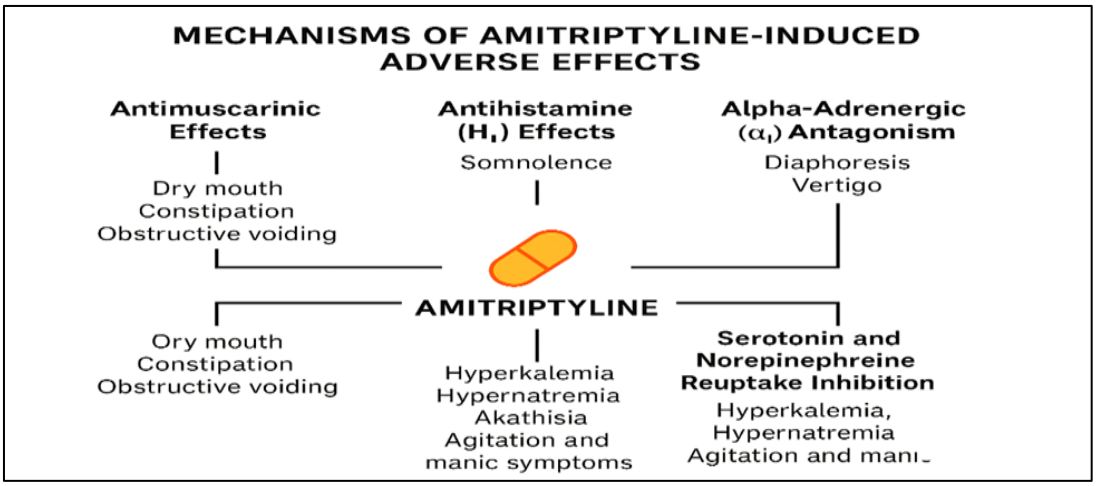

Figure 1 The proposed mechanism underlying the adverse drug reactions

2. Methodology

This case series was compiled from reports submitted to the Adverse Drug Reaction Monitoring Centre (AMC) at Believers Church Medical College Hospital. Cases included patients prescribed amitriptyline who developed multisystem adverse effects during treatment. Each case was assessed using the following standardized tools:

- **Causality:** WHO-UMC Causality Assessment Scale
- **Severity:** Modified Hartwig's Severity Assessment Scale
- **Type of Reaction:** Rawlins and Thompson Classification
- **Preventability:** Schumock and Thornton Preventability Scale
- **Seriousness:** WHO criteria

Patient details were anonymized, and written consent was obtained. All cases were analyzed for drug indication, dose, time of onset, recovery following withdrawal, and clinical outcomes.

3. Results

A total of six cases were reported to the ADR Monitoring Centre over a 12-month period (January 2024–January 2025) involving suspected adverse drug reactions attributed to amitriptyline. The patients ranged in age from 23 to 77 years, with an even distribution of genders (3 females, 3 males). All patients were on amitriptyline for various clinical indications including sleep disturbances, fibromyalgia, depression, neuralgic pain, and obsessive-compulsive disorder.

Case 1: A 55-year-old male developed dry mouth and constipation after prolonged use (over 3 years) of low-dose amitriptyline (12.5 mg). Symptoms gradually worsened and were unrelated to any new medication, dietary, or lifestyle changes. Discontinuation of the drug led to symptom resolution within days.

Case 2: A 72-year-old female on amitriptyline for fibromyalgia developed **akathisia**—a movement disorder characterized by restlessness—approximately one year after initiating therapy. The symptom was disturbing enough to impair daily function but resolved after drug withdrawal.

Case 3: A 77-year-old female presented with excessive daytime sleepiness despite being on a low dose (10 mg). No other sedatives were newly introduced. After reducing the dose to 5 mg, the patient showed marked improvement in alertness and quality of life.

Case 4: A 75-year-old male developed progressive urinary hesitancy and incomplete bladder emptying, attributed to amitriptyline's anticholinergic action. The ADR mimicked symptoms of benign prostatic hyperplasia but improved upon stopping the drug.

Case 5: A 77-year-old female developed vertigo shortly after starting amitriptyline for depression. There were no other identifiable causes, such as vestibular disease or recent head trauma. Discontinuation resulted in gradual improvement.

Case 6: A 23-year-old female with a history of Major Depressive Disorder and OCD developed sudden-onset aggression and manic symptoms within 24 hours of starting amitriptyline. Symptoms resolved rapidly upon discontinuation, confirming a strong temporal relationship.

All six cases were classified as "Type A" (augmented, predictable) ADRs based on Rawlins and Thompson classification. Causality was assessed as "Probable" in all cases using the WHO-UMC scale. Severity was assessed as Level 2 for most cases, except for Case 6, which reached Level 3 due to the need for clinical monitoring post-withdrawal. All cases were deemed "Probably Preventable" based on the Schumock and Thornton scale.

4. Discussion

Amitriptyline continues to be widely prescribed due to its proven efficacy in managing neuropathic pain, insomnia, and depressive symptoms. However, the cases discussed in this series illuminate a troubling but underappreciated aspect of this drug—its potential to cause multisystem toxicity even at low doses, and especially in populations at higher risk, such as the elderly or polypharmacy patients.

The anticholinergic burden of amitriptyline is well documented. Case 1, involving dry mouth and constipation, demonstrates how these effects can persist unnoticed over time, subtly impairing quality of life [5,14]. Elderly patients often attribute such symptoms to aging or comorbidities, allowing ADRs to remain undiagnosed. The issue is compounded by the fact that constipation in diabetics, like our patient, could also be wrongly attributed to autonomic neuropathy.

Akathisia, as seen in Case 2, is an often-misdiagnosed movement disorder that causes internal restlessness. It is more commonly associated with antipsychotics but has been reported with TCAs as well [6,15]. Its presentation can be mistaken for anxiety or progression of fibromyalgia, delaying appropriate management.

Somnolence, illustrated in Case 3, is particularly relevant in geriatrics, where even mild sedation can increase the risk of falls, confusion, and loss of independence [5,7,16]. Given the polypharmacy and comorbid status of many older adults, amitriptyline's sedative effects need constant reassessment. The patient's improvement with dose reduction underscores the need for titrated regimens based on tolerance and age-related pharmacokinetics.

Case 4 involved obstructive voiding, a side effect rarely attributed to antidepressants but entirely explainable via amitriptyline's anticholinergic action on the detrusor muscle. Symptoms mimicked a urological disorder, risking unnecessary evaluations or interventions. In older men, such symptoms could worsen pre-existing prostate enlargement, making it imperative for prescribers to differentiate pharmacological causes from structural ones [17].

Case 5 demonstrated vertigo, a less commonly discussed effect but one that dramatically affects functional capacity in the elderly. The mechanism could involve orthostatic hypotension, vestibular suppression, or central nervous system effects—all linked to amitriptyline's widespread receptor activity [18].

The most severe presentation was in Case 6, where a young female with MDD developed acute manic symptoms within 24 hours of initiating therapy. Tricyclic antidepressants are known to precipitate mania in susceptible individuals, particularly those with undiagnosed bipolar disorder or high serotonergic sensitivity [11,12,17]. The rapid resolution following drug withdrawal suggests a high degree of certainty in the causal relationship. This case underscores the necessity of psychiatric screening and close monitoring in the early phases of antidepressant therapy.

Collectively, these cases reflect the unpredictability of ADRs, especially in real-world settings where patients have complex health backgrounds. Despite being "old," amitriptyline has a broad pharmacodynamic profile that predisposes to cognitive impairment, urinary retention, cardiovascular changes, and behavioral disturbances [1,5,9]. The pharmacogenomic variability in CYP2D6 and CYP2C19 metabolism further complicates its predictability in different individuals [19].

In an era emphasizing personalized medicine, amitriptyline should not be used as a default treatment. The Beers Criteria (2023) and other deprescribing guidelines now caution against the routine use of TCAs in the elderly due to increased risk of falls, confusion, and anticholinergic load [12]. Safer alternatives such as duloxetine, gabapentinoids, or SSRIs with better tolerability profiles should be considered, especially when treating chronic pain or depression in older adults.

5. Conclusion

These case series illustrate that while amitriptyline provides symptomatic relief, its use requires caution, especially in vulnerable populations. The drug's adverse effects, although predictable, are often underrecognized and misattributed to comorbid conditions or aging. Regular medication reviews, individualized dosing, and active pharmacovigilance can mitigate these risks. By increasing awareness and early identification of ADRs, healthcare providers can make more informed decisions about the continuation or discontinuation of amitriptyline. The ultimate goal should be to preserve the patient's safety, functionality, and quality of life.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript, and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Statement of ethical approval

Ethical board approval was not needed as the data were anonymized and collected as part of routine pharmacovigilance practice without direct patient contact. All ethical principles outlined in the Declaration of Helsinki were followed.

Statement of informed consent

Individual patient consent was not required as this case series is based on spontaneously reported cases in the institutional pharmacovigilance database.

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