**MITOCHONDRIAL DYSFUNCTION IN CHLORPROMAZINE NEURODEGENERATION**

**Abstract:**

 Chlorpromazine CPZ, a widely used antipsychotic, has been linked to neurological side effects, including tardive dyskinesia, and evidence suggests a potential for long-term neurotoxic effects. This review synthesizes findings from in vitro and in vivo studies investigating the impact of CPZ exposure on mitochondrial bioenergetics, oxidative stress, mitochondrial dynamics, and mitophagy. Studies were identified through comprehensive searches of databases such as PubMed, Scopus, and Web of Science using relevant keywords. The available literature indicates that CPZ can disrupt mitochondrial function, leading to decreased ATP production, increased reactive oxygen species (ROS) generation, impairments in mitochondrial fusion and fission, and altered mitophagy. These disruptions contribute to neuronal damage and cell death. Further investigation is crucial to fully elucidate the mechanisms by which CPZ affects mitochondrial integrity and contributes to neurodegeneration. This review highlights the importance of mitochondrial dysfunction as a key pathological mechanism in CPZ-induced neurotoxicity. Understanding these pathways may provide valuable insight for developing strategies to mitigate the neurodegenerative potential of CPZ and related antipsychotic medications.

**Keywords:** *Chlorpromazine, Neurodegeneration, Mitochondria, Mitochondrial Dysfunction, Oxidative Stress,*

**INTRODUCTION**

Chlorpromazine (CPZ), a first-generation antipsychotic drug introduced in the mid-20th century, revolutionized the treatment of schizophrenia and other psychotic disorders (Iliuță et al., 2024). For decades, it has served as a cornerstone medication for managing positive symptoms like hallucinations and delusions. However, the widespread use of CPZ is complicated by a significant concern: its potential to induce a range of adverse effects, including the particularly worrisome possibility of neurotoxicity (Pulkrabkova et al., 2023; Deb et al., 2023). This review aims to delve into the compelling link between CPZ exposure and neurodegeneration, a progressive and often irreversible process characterized by the loss of neuronal structure and function, ultimately leading to cognitive and motor impairments (Yagami et al., 2019). Specifically, this mini-review address the critical problem of CPZ-induced neurotoxicity and its potential association with long-term neurological complications like tardive dyskinesia, cognitive deficits, and other extrapyramidal symptoms. While the precise mechanisms underlying this neurotoxic effect remain under investigation, this review posits that mitochondrial dysfunction plays a significant and potentially causative role in the complex cascade of events leading to CPZ-induced neurodegeneration. The study hypothesize that CPZ's interference with mitochondrial processes, such as oxidative phosphorylation and calcium homeostasis, initiates a chain reaction that ultimately damages and destroys vulnerable neuronal populations.

The scope of this review encompasses an examination of the existing literature outlining the neurotoxic effects of CPZ, drawing from in vitro studies, in vivo animal models, and clinical observations. The study will pay particular emphasis on elucidating the intricate mechanisms through which CPZ disrupts mitochondrial function, analyzing its effects on mitochondrial membrane potential, reactive oxygen species (ROS) production, and mitochondrial biogenesis. Furthermore, the review explore the potential interplay between mitochondrial dysfunction and other downstream consequences of CPZ exposure, such as oxidative stress, inflammation, and altered proteostasis. The objective is to synthesize the current scientific evidence to provide an understanding of the role mitochondria play in mediating the neurodegenerative consequences of CPZ exposure. By clarifying the underlying mechanisms, this review aims to identify potential therapeutic targets and strategies to mitigate CPZ-induced neurotoxicity and improve the long-term outcomes for patients requiring antipsychotic treatment. Ultimately, this knowledge could inform the development of safer and more effective antipsychotic medications or adjunctive therapies that protect neuronal health and prevent the debilitating neurological sequelae associated with prolonged CPZ use.

**BACKGROUND INFORMATION**

**A. Chlorpromazine (CPZ)**

Chlorpromazine (CPZ), a phenothiazine derivative, stands as a landmark antipsychotic medication, historically significant for revolutionizing the treatment of schizophrenia. Its chemical structure features a three-ring system with a side chain containing a tertiary amine, contributing to its amphiphilic nature and ability to interact with a variety of receptors (Ashkar et al., 2024; Bhatnagar and Pemawat, 2022; Matteoni et al., 2021). CPZ's antipsychotic effects arise primarily from its antagonism of dopamine D2 receptors in the mesolimbic pathway of the brain, effectively reducing positive symptoms like hallucinations and delusions (Panov and Panova, 2024; Mlambo et al., 2023). Following administration, CPZ undergoes extensive metabolism in the liver, primarily via oxidation and conjugation, resulting in numerous metabolites with varying levels of activity. Its distribution is widespread due to its lipophilicity, allowing it to cross the blood-brain barrier and accumulate in fatty tissues. While effective, CPZ is also associated with a range of side effects, notably neurological effects such as extrapyramidal symptoms (EPS) including dystonia, akathisia, Parkinsonism and tardive dyskinesia, stemming from its dopamine receptor blockade. Other neurological side effect include sedation, cognitive impairment and potentially neuroleptic malignant syndrome, a rare but life-threatening condition (Morgan et al., 2019).

**B. Mitochondria: Structure and Function**

Mitochondria, often hailed as the powerhouses of the cell, are essential organelles responsible for a multitude of critical cellular processes. Their intricate structure directly supports their diverse functions. Each mitochondrion is enclosed by a double membrane system: a smooth outer membrane and a highly convoluted inner membrane. These folds, known as cristae, significantly increase the surface area available for key biochemical reactions. The space enclosed by the inner membrane is the mitochondrial matrix, which houses enzymes, ribosomes, and mitochondrial DNA. Beyond energy production, mitochondria play pivotal roles in maintaining cellular health, including calcium homeostasis, regulating the production of reactive oxygen species (ROS) while also providing antioxidant defense, and controlling apoptosis, or programmed cell death. Furthermore, mitochondria are not static entities; they undergo constant dynamic processes of fusion (joining together), fission (splitting apart), and mitophagy (selective degradation of damaged mitochondria), allowing for adaptation to changing cellular needs and ensuring the overall health of the mitochondrial network (Oyovwi et al.,2024; Mendelsohn et al., 2022; Giacomello et al., 2020; Dorn, 2019).

**MATERIALS AND METHOD**

The study primarily involved a literature search. The review utilized databases such as PubMed, Scopus, and Web of Science to identify relevant articles. Original research articles and reviews that investigated the effects of chlorpromazine on mitochondrial function in neuronal cells or animal models were included. Studies focusing solely on other cell types or lacking relevance to neurodegeneration were excluded. Data extraction focused on identifying key mechanisms of mitochondrial dysfunction induced by chlorpromazine, including effects on mitochondrial membrane potential, reactive oxygen species production, calcium homeostasis, and apoptosis pathways. The extracted information was then synthesized and critically analyzed to provide a concise overview of the current understanding of chlorpromazine-induced mitochondrial impairments in the context of neurodegeneration.

**EVIDENCE FOR MITOCHONDRIAL DYSFUNCTION IN CPZ-INDUCED NEURODEGENERATION**

**Compelling evidence implicates mitochondrial dysfunction as a key driver of chlorpromazine (CPZ)-induced neurodegeneration, a process characterized by the progressive loss of structure and function of neurons (**Mukherjee et al., 2025; De Simone et al., 2023; Wu et al., 2019)**.** Chlorpromazine, a first-generation antipsychotic medication, has been associated with a range of adverse effects, including neurological complications (Leucht et al., 2024; Zareifopoulos et al., 2021). A growing body of research suggests that these complications are, at least in part, due to the drug's detrimental impact on mitochondria, the powerhouses of the cell (Leucht et al., 2024; Zareifopoulos et al., 2021). **Studies have consistently demonstrated that CPZ exposure impairs mitochondrial respiration and ATP production, essential processes for cellular energy generation and survival.** This deleterious effect manifests in several ways. **This is evidenced by decreased oxygen consumption in CPZ-treated cells and animals, indicating a reduced capacity of the mitochondria to utilize oxygen for energy production. This is further supported by impaired electron transport chain (ETC) activity, a crucial set of protein complexes within the mitochondria responsible for transferring electrons and generating a proton gradient that drives ATP synthesis.** This disruption of the ETC ultimately leads to reduced ATP synthesis and subsequent energy depletion, leaving neurons vulnerable to cellular stress and eventual cell death (Abbruzzese et al., 2023; Matteoni et al., 2021; Luo et al., 2020).

**Furthermore, CPZ induces oxidative stress within neurons, characterized by increased levels of reactive oxygen species (ROS) and depletion of crucial antioxidant defenses such as glutathione.** ROS, harmful byproducts of cellular metabolism, can cause significant damage to cellular components if not effectively neutralized by antioxidant systems. CPZ appears to exacerbate ROS production while simultaneously impairing the cell's ability to combat oxidative stress. **This oxidative burden results in lipid peroxidation (damage to cell membranes), protein oxidation (altering protein structure and function), and DNA damage, further compromising neuronal health and contributing to cellular dysfunction.** **CPZ also disrupts mitochondrial calcium homeostasis, causing calcium overload within the mitochondria, impacting mitochondrial membrane potential, and ultimately activating calcium-dependent cell death pathways (**Madireddy and Madireddy, 2023; Enye et al., 2021)**.** Mitochondria play a critical role in regulating calcium levels within the cell. CPZ disrupts this delicate balance, leading to an excessive accumulation of calcium within the mitochondria. This calcium overload disrupts the mitochondrial membrane potential, a key factor in energy production, and triggers calcium-dependent signaling cascades that activate programmed cell death pathways, such as apoptosis (Matuz-Mares et al., 2022).

**The impact of CPZ extends to mitochondrial dynamics, influencing mitochondrial morphology (fragmentation or elongation), altering rates of fusion and fission, and impairing mitophagy, which results in the accumulation of damaged mitochondria.** Mitochondria are highly dynamic organelles, constantly undergoing fusion (joining together) and fission (dividing). These processes are essential for maintaining a healthy mitochondrial network and adapting to cellular needs. CPZ disrupts these processes, leading to either excessive fragmentation or elongation of mitochondria, both of which can impair their function. Furthermore, CPZ impairs mitophagy, a process by which damaged mitochondria are selectively removed and recycled. This leads to the accumulation of dysfunctional mitochondria, further exacerbating cellular stress and contributing to neurodegeneration (Green et al., 2022). **In vivo studies using animal models of CPZ-induced neurotoxicity, alongside limited clinical data, further support the correlation between CPZ exposure and mitochondrial dysfunction in brain tissue, solidifying the role of mitochondrial compromise in CPZ-mediated neurodegeneration.** Animal models provide a valuable platform for studying the effects of CPZ on the brain, and these studies consistently demonstrate that CPZ exposure leads to mitochondrial dysfunction in various brain regions. While clinical data is limited, it does provide further evidence suggesting a link between CPZ exposure and mitochondrial abnormalities in humans. Taken together, these findings strongly suggest that mitochondrial dysfunction plays a critical role in the neurodegenerative effects observed with CPZ use, highlighting the need for further research to understand the underlying mechanisms and develop potential therapeutic interventions to protect against CPZ-induced mitochondrial damage and neurodegeneration (Wyse et al., 2021; Kundap et al., 2020; Andrew et al., 2017).

**MECHANISMS UNDERLYING CPZ-INDUCED MITOCHONDRIAL DYSFUNCTION**

**Chlorpromazine (CPZ), has been implicated in mitochondrial dysfunction through a variety of mechanisms, raising concerns about its long-term effects and potential for inducing or exacerbating metabolic and neurological issues (**Chan et al., 2020)**.** This dysfunction manifests as a decreased capacity of mitochondria to generate energy and maintain cellular homeostasis. One key pathway involves the direct interaction of CPZ with mitochondrial components, essentially a molecular interference within the powerhouses of the cell. **This includes the binding of CPZ molecules to specific mitochondrial proteins, particularly those within the electron transport chain (ETC) complexes (I, II, III, IV, and ATP synthase), the core machinery responsible for generating ATP.** By binding to these proteins, CPZ can potentially disrupt their function, altering their conformational structure or interfering with electron transfer, thereby impairing ATP production and leading to cellular energy deficits. Furthermore, CPZ can alter the permeability of the mitochondrial membrane, specifically the inner mitochondrial membrane (IMM), which is crucial for maintaining the proton gradient. **An increase in permeability causes a leak of protons back across the membrane, leading to the dissipation of the proton gradient essential for oxidative phosphorylation, the process driving ATP synthesis.** This uncoupling effect forces the ETC to work harder to maintain the gradient, further stressing the mitochondria and potentially leading to increased reactive oxygen species (ROS) production (Zong et al., 2024; Stoker et al., 2019).

Beyond these direct effects, CPZ can also trigger indirect mechanisms that contribute to mitochondrial toxicity, amplifying the initial insult. **CPZ-induced inflammation, whether systemic or localized within specific tissues, can release inflammatory cytokines and mediators that have a detrimental impact on mitochondrial health.** These inflammatory signals can impair mitochondrial biogenesis, increase oxidative stress, and promote mitochondrial degradation (mitophagy) in a damaging manner. **Furthermore, CPZ metabolites, the breakdown products of the drug within the body, may themselves possess toxic properties that compromise mitochondrial function.** Some metabolites may accumulate within mitochondria, exacerbating direct binding effects or interfering with other metabolic pathways within the organelle. **Additionally, CPZ may interact with other cellular pathways, such as the endoplasmic reticulum (ER) stress response, which can indirectly affect mitochondria due to the close interplay between these organelles.** ER stress, triggered by the accumulation of unfolded or misfolded proteins within the ER, can initiate a cascade of signaling events that ultimately impact mitochondrial function. For instance, prolonged ER stress can lead to increased ROS production, calcium dysregulation, and the activation of apoptotic pathways, all of which can compromise mitochondrial integrity and function. The mitochondrial-ER interaction highlights the intricate network of cellular processes involved in CPZ-induced toxicity. **Understanding these complex and interconnected mechanisms – the direct binding, membrane disruption, inflammatory responses, metabolite toxicity, and indirect effects via the ER stress response – is crucial for developing strategies to mitigate CPZ-induced mitochondrial dysfunction and its associated adverse effects.** This knowledge can inform the development of novel therapeutic interventions, such as antioxidant therapies, mitochondrial protectants, or strategies to modulate ER stress, to improve patient outcomes and minimize the risks associated with long-term CPZ use. Further research is needed to fully elucidate the specific mitochondrial targets of CPZ and the precise mechanisms through which it exerts its toxic effects (Land et al., 2023; Li et al., 2022).

**POTENTIAL THERAPEUTIC STRATEGIES**

Addressing chlorpromazine (CPZ)-induced mitochondrial toxicity necessitates a multifaceted therapeutic approach carefully designed to address the various pathways and mechanisms through which CPZ exerts its harmful effects. Recognizing that CPZ disrupts multiple aspects of mitochondrial function, researchers are exploring several potential strategies to mitigate its detrimental consequences, aiming to restore mitochondrial health and function (Zuo et al., 2024;

**Antioxidant Therapies:** Chlorpromazine (CPZ) exposure initiates a detrimental cascade of oxidative stress within mitochondria, the powerhouses of the cell. This process leads to the overproduction of damaging reactive oxygen species (ROS), highly unstable molecules with unpaired electrons. These ROS, including superoxide radicals and hydrogen peroxide, can attack and damage cellular components. Antioxidant therapies are designed to counteract this oxidative stress by neutralizing these free radicals and restoring the delicate redox balance within the mitochondria and the cell as a whole. This therapeutic approach involves the administration of potent antioxidants, such as Vitamin E (alpha-tocopherol), a lipid-soluble antioxidant known for its ability to protect cell membranes from lipid peroxidation, and coenzyme Q10 (CoQ10), also known as ubiquinone, a crucial component of the electron transport chain. CoQ10 not only participates in energy production but also possesses significant antioxidant capabilities, quenching free radicals directly and regenerating other antioxidants like Vitamin E. These agents work synergistically to scavenge free radicals, preventing or minimizing damage to critical mitochondrial components, including the mitochondrial membranes (both inner and outer), mitochondrial DNA (mtDNA), and essential proteins involved in energy production and cellular function. By protecting these structures, antioxidant therapies aim to preserve mitochondrial function, reduce cellular damage, and potentially mitigate the adverse effects of CPZ exposure. Furthermore, some antioxidants can also promote the expression of endogenous antioxidant enzymes, further bolstering the cell's defense against oxidative stress (De Simone et al., 2023; Mani et al., 2022).

**Mitochondrial Protectants:** Beyond simply addressing oxidative stress, efforts are focused on directly bolstering mitochondrial function and resilience. This proactive approach aims to fortify these cellular powerhouses from within, ensuring they can withstand age-related decline and environmental stressors. Mitochondrial protectants, such as low-dose mitochondrial uncouplers, are being investigated for their ability to gently increase proton leak across the inner mitochondrial membrane. This subtle uncoupling can reduce the electrochemical gradient, leading to decreased Reactive Oxygen Species (ROS) production and potentially improving mitochondrial efficiency in the long run. While seemingly counterintuitive, controlled uncoupling can optimize energy production and reduce damaging byproducts. Nicotinamide riboside (NR), a precursor to nicotinamide adenine dinucleotide (NAD+), is another promising avenue in mitochondrial protection. By increasing NAD+ levels, which naturally decline with age, NR can enhance mitochondrial biogenesis (the creation of new mitochondria), improve mitochondrial respiratory function (the efficiency of energy production), and promote overall mitochondrial health. This ultimately contributes to cellular energy maintenance and potentially extends healthy lifespan. These strategies represent a shift towards actively supporting mitochondrial health rather than solely mitigating damage, offering a more comprehensive approach to combatting age-related diseases and enhancing overall well-being (Oyovwi et al., 2024; Hubbard et al., 2018).

**Calcium Regulation:** Chlorpromazine (CPZ) can significantly disrupt the delicate balance of calcium ions within cells, a process known as calcium homeostasis. Specifically, CPZ can induce an excessive accumulation of calcium within the mitochondria, the cell's powerhouse responsible for energy production. This mitochondrial calcium overload is not benign; it can trigger a cascade of events leading to mitochondrial dysfunction, compromising the organelle's ability to generate energy and maintain its integrity. Ultimately, this dysfunction can initiate cell death pathways, such as apoptosis. To mitigate or prevent these detrimental effects, researchers are exploring the use of calcium channel blockers as a means to precisely regulate mitochondrial calcium levels. Calcium channel blockers act by inhibiting the influx of calcium ions into the mitochondria, effectively reducing the amount of calcium accumulating within the organelle. By controlling this influx, these agents can help maintain proper calcium balance within the mitochondria, preventing the overload that triggers downstream apoptotic pathways and cell death. This regulation holds promise for protecting cells from the damaging effects of CPZ and potentially other conditions that lead to mitochondrial calcium overload (McCarthy et al., 2023; Chu et al., 2022).

**Mitophagy Enhancers:** Damaged mitochondria are a significant contributor to cellular dysfunction, aging, and inflammation. These compromised organelles can leak reactive oxygen species (ROS), disrupt energy production, and trigger inflammatory signaling pathways, ultimately contributing to a range of diseases. Mitophagy, a selective and crucial form of autophagy, acts as the cell's quality control mechanism for mitochondria. It's the process by which damaged or dysfunctional mitochondria are specifically identified, tagged, and then engulfed by autophagosomes for degradation and recycling of their components. Mitophagy enhancers represent a promising therapeutic avenue for addressing the detrimental effects of mitochondrial damage. These are compounds or interventions designed to stimulate the mitophagy pathway, thereby accelerating the selective clearance of compromised mitochondria and promoting a healthier, more efficient mitochondrial population. By enhancing mitophagy, we can reduce the build-up of ROS, minimize inflammatory signals, and improve overall cellular energy production. Current research is intensely focused on identifying and developing compounds and strategies that effectively stimulate mitophagy pathways. This includes exploring natural compounds, pharmacological agents, and even genetic interventions. The goal is to achieve the efficient and targeted removal of dysfunctional mitochondria, preventing the accumulation of potentially harmful mitochondrial debris and ultimately contributing to improved cellular health and disease prevention. Understanding the intricate mechanisms of mitophagy and developing effective enhancers holds immense potential for combating age-related diseases, neurodegenerative disorders, and metabolic syndromes, all of which are linked to mitochondrial dysfunction (Evans and Holzbaur, 2020; Sedlackova et al., 2019).

**Targeting Chlorpromazine (CPZ) Metabolism:** A long-term therapeutic strategy centers on directly intervening in the complex metabolism of CPZ itself. Recognizing that CPZ's toxicity stems largely from the formation of harmful metabolites, a deeper understanding of the specific metabolic pathways involved is crucial. Researchers are focusing on identifying and characterizing these pathways, particularly those that lead to the generation of toxic CPZ byproducts. The ultimate goal is to develop targeted interventions that can effectively reduce the production of these detrimental metabolites. Several approaches are being explored within this strategy. One involves inhibiting specific enzymes that play a key role in the formation of the toxic metabolites. By selectively blocking these enzymes, the production of harmful byproducts could be significantly reduced. Another approach focuses on promoting alternative metabolic pathways that lead to the generation of less toxic or even inert compounds. This could involve manipulating the metabolic machinery within the cell to favor pathways that detoxify CPZ. The potential advantage of this upstream intervention is significant. By minimizing the initial formation of toxic metabolites, we can potentially reduce the initial insult to vital cellular components like the mitochondria, a major target of CPZ-induced toxicity. This, in turn, could lessen the severity of downstream cellular damage and ultimately reduce the need for more complex and potentially less effective therapeutic interventions that address the consequences of CPZ metabolism rather than the root cause. This proactive approach holds promise for developing more effective and preventative therapies for CPZ-related toxicity in the long run (Wei et al., 2023; He et al., 2022).

**CONCLUSION**

In conclusion, the mounting evidence overwhelmingly supports the proposition that mitochondrial dysfunction is a key driver in chlorpromazine (CPZ)-induced neurodegeneration. A wealth of in vitro and in vivo studies have consistently and convincingly demonstrated that exposure to CPZ triggers a cascade of detrimental effects on mitochondria within neuronal cells. Specifically, these studies reveal that CPZ exposure leads to: (1) impaired mitochondrial respiration, resulting in reduced energy production and cellular dysfunction; (2) increased oxidative stress, driven by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, leading to damage to cellular components; (3) disrupted calcium homeostasis, characterized by abnormal calcium levels within mitochondria and the cytoplasm, crucial for neuronal signaling and survival; and (4) altered mitochondrial dynamics, including aberrant fusion, fission, and mitophagy processes, impacting mitochondrial health and network integrity. These interconnected disruptions ultimately culminate in cellular damage, including DNA damage, protein misfolding, and ultimately, neuronal loss, contributing to the neurotoxic effects observed with CPZ treatment.

While the current body of evidence paints a compelling and largely consistent picture, significant gaps remain in our understanding. Further research is crucial to fully elucidate the precise molecular mechanisms by which CPZ directly and indirectly targets and disrupts mitochondrial function. This includes identifying the specific proteins and pathways involved in CPZ-induced mitochondrial damage and understanding how these disruptions translate into specific neurotoxic phenotypes. A deeper understanding of these processes, including the temporal sequence of events and the specific vulnerability of different neuronal populations, is essential for developing targeted therapeutic strategies aimed at protecting vulnerable neuronal populations from CPZ-induced damage. Future research should prioritize several key areas. First, identifying specific mitochondrial proteins that serve as direct or indirect targets of CPZ is paramount. This could involve proteomic analyses, targeted mutagenesis studies, and investigations of CPZ binding to mitochondrial components. Second, research should explore the potential of mitochondrial-targeted antioxidants or calcium regulators to mitigate CPZ-induced mitochondrial dysfunction. This includes evaluating the efficacy of existing compounds and developing novel agents specifically designed to protect mitochondria from oxidative stress and calcium overload. Third, investigations into the efficacy of novel neuroprotective agents, including those targeting inflammation, apoptosis, and autophagy, are warranted in preclinical models of CPZ-induced neurotoxicity. These models should encompass both in vitro cellular models and in vivo animal models that recapitulate the key features of CPZ-related neurotoxicity. Finally, translational studies are needed to explore potential biomarkers of CPZ-induced mitochondrial dysfunction in patients undergoing CPZ treatment. This will pave the way for the development of effective therapies to mitigate the neurological side effects associated with CPZ treatment, improve patient outcomes, and enhance the quality of life for individuals requiring this medication. Furthermore, understanding the mechanisms of CPZ-induced neurotoxicity may offer insights into the pathogenesis of other neurodegenerative disorders involving mitochondrial dysfunction.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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