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**Fatal Serotonin Syndrome: A Systematic Review of 56 Cases in the Literature**

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**Abstract**

**Introduction:** Serotonin syndrome (SS) is a drug-induced potentially life-threatening clinical condition. There is a paucity of data on the risk factors, clinical course, and complications associated with fatal SS.

**Objective:** To characterize the epidemiological profile, clinical features, and risk factors associated with fatal SS through a systematic review.

**Methods:** We performed a systematic review of MEDLINE and Google Scholar for case reports, case series, or cohort studies of fatal SS.

**Results:** Initial database search identified 2326 articles of which 46 (56 patients) were included in the final analysis. The mean age was 42.3 years (range 18-87 years) with female predominance (57%). North America and Europe constitute 80% of the reported fatal SS. The symptoms evolved very rapidly, within 24 h after the administration of serotonergic drugs in 59% of the cases. Fever (61%) was the most common symptom, followed by seizure (36%) and tremors (30%). The mean temperature in the reported cases (25 patients) was 41.6 ± 1.3 °C (range 38.3-43.5 °C). SS was reported to occur with the maintenance dosage of serotonergic agents, after initiation of the drug for the first time, and addition of the drugs for the development of another unrelated illness. Creatine kinase (CK) activities were elevated (>3 times of the upper limit of normal) in eighteen patients, and it was very high (>25,000 IU/L) in four patients. Presence of high grade fever, seizures, and high CK activities may be associated with severe SS. Nine patients (16%) received 5-HT2A antagonists as a therapy. About 50% of patients died within 24 h of the onset of symptoms.

**Conclusions:** While Fatal SS Is Rare, Frequently Observed Features Include Hyperthermia, Seizures, And High CK Activities. Cyproheptadine Use Appears Infrequent For These Patients.

**Keywords:** Serotonin Syndrome; Cyproheptadine; Serotonin; Serotonin Toxicity.