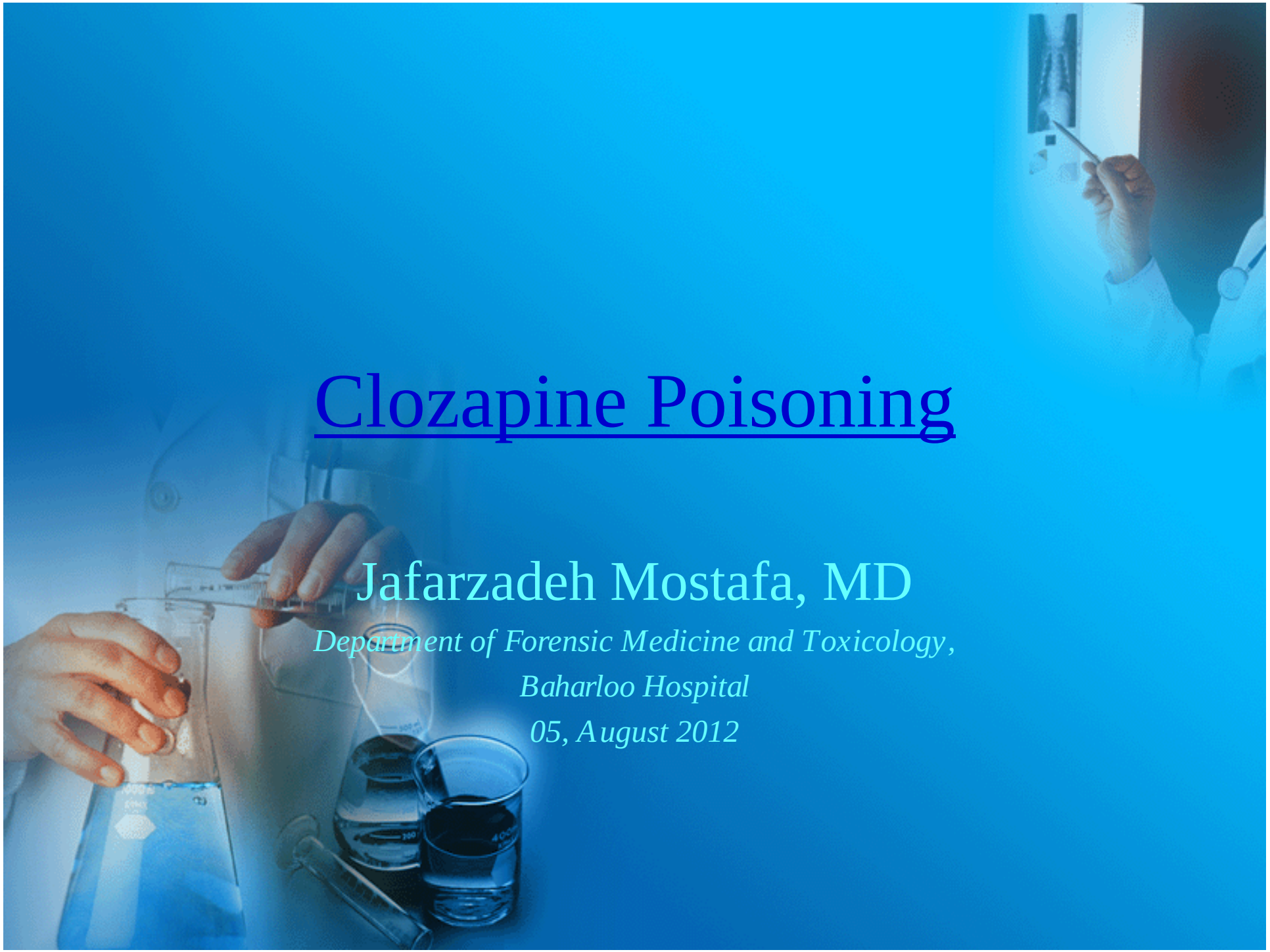

Clozapine Poisoning

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Clozapine

- the first atypical antipsychotic medication
- treat the symptoms of schizophrenia
- not associated with the risk of extrapyramidal syndrome
- the gold standard treatment for refractory patients with severe psychotic disorders

Clozapine

- Direct muscarinic antagonist
- α-Adrenoceptor antagonists
- Dopamine antagonism
- Serotonin antagonism
- Indirect $GABA_A$ antagonists
- Glycine uptake inhibitor
- Glutamate uptake inhibitor

Clozapine

Usual Daily Adult Dose (mg)	Volume of Distribution (L/kg)	Half-Life (Range, h)	Protein Binding (%)
50–900	5.4 ± 3.5	6–17	95

Side effects

- Drowsiness
- Dizziness
- Increased salivation
- Constipation
- Dry mouth
- Restlessness
- Headache

Agranulocytosis

- Shortly after its introduction in Finland in 1975, 18 patients developed severe neutropenia and 8 of them died
- Clozapine-induced agranulocytosis is associated with the HLA B38, DR4, and DQ3 haplotypes, underlining a genetic predisposition to acquired aplastic anemia.

Adverse effects with life-threatening potential

- agranulocytosis and neutropenia
- Myocarditis
- Cardiomyopathy
- Pericarditis
- Alveolitis
- Pancreatitis
- Hepatitis
- Nephritis
- Colitis
- drug-induced lupus erythomatosus
- status epilepticus
- diabetic ketoacidosis and hyperosmolar coma
- neuroleptic malignant syndrome

IMPORTANT WARNINGS

- shaking hands that you cannot control
- seizures
- fainting
- difficulty urinating or loss of bladder control
- confusion
- changes in vision
- shakiness
- fever
- severe muscle stiffness
- sweating
- confusion
- changes in behavior
- sore throat
- unusual bleeding or bruising
- loss of appetite
- upset stomach
- yellowing of the skin or eyes
- pain in the upper right part of the stomach
- flu-like symptoms
- lack of energy

Overdose

- dizziness
- fainting
- slow breathing
- change in heartbeat
- loss of consciousness

TABLE 67–3. Adverse Effects of Antipsychotics

CNS	Somnolence, coma
	Respiratory depression or loss of airway reflexes
	Hyperthermia
	Seizures
	Extrapyramidal syndromes
	Central anticholinergic syndrome
Cardiovascular	
Clinical	Tachycardia
	Hypotension (orthostatic or resting)
	Myocardial depression
Electrocardiographic	QRS complex widening
	Right deviation of terminal 40 msec of frontal plane axis
	QTc prolongation
	Torsades de pointes
	Nonspecific repolarization changes
Endocrine	Amenorrhea, oligomenorrhea, or metrorrhagia
	Breast tenderness and galactorrhea
Gastrointestinal	Impaired peristalsis
	Dry mouth
Genitourinary	Urinary retention
	Ejaculatory dysfunction
	Priapism
Ophthalmic	Mydriasis or miosis
	Visual blurring
Dermatologic	Impaired sweat production
	Cutaneous vasodilation

DIAGNOSTIC TESTS
in antipsychotic poisoning

- clinical history
- physical examination

- Both the clinical and ECG findings described above are nonspecific and can occur following overdose of several different drug classes, including TCAs, skeletal muscle relaxants, carbamazepine, and first-generation antihistamines.
- the absence of typical ECG changes does not exclude a significant antipsychotic ingestion.
- Plasma concentrations of antipsychotics are not widely available, do not correlate well with clinical signs and symptoms, and do not help guide therapy.
- Blood and urine immunoassays for TCAs may yield a false positive in the presence of phenothiazines

MANAGEMENT

- Supportive care is the cornerstone of treatment for patients with antipsychotic overdose.
- Supplemental oxygen if hypoxia is present
- thiamine, naloxone, and parenteral dextrose as needed in patients with altered mental status
- continuous cardiac monitoring.
- **Asymptomatic patients with normal ECGs 6 hours following exposure are at exceedingly low risk of complications and no longer require cardiac monitoring.**
- **Symptomatic patients and those with abnormal ECGs should have continuous monitoring for a minimum of 24 hours**

MANAGEMENT

- Gastrointestinal Decontamination
  - For patients who present within a few hours of a large or polydrug overdose
  - Induced emesis is absolutely contraindicated
  - Orogastric lavage and whole-bowel irrigation are unlikely to be necessary in the absence of coingestants.

MANAGEMENT

- Treatment of Cardiovascular Complications
  - 0.9% sodium chloride solution for hypotension
  - direct-acting agonists, such as norepinephrine or phenylephrine, are preferred over dopamine.
  - Sodium bicarbonate (1–2 mEq/kg) for progressive widening of the QRS
    - Target blood pH of 7.5. If the patient is intubated
  - lidocaine (1–2 mg/kg followed by continuous infusion) as second-line antidysrhythmic

MANAGEMENT

- Treatment of Seizures
  - generally short-lived and often require no pharmacologic treatment
  - Multiple or refractory seizures can be treated with benzodiazepines

MANAGEMENT

- Treatment of the Central Antimuscarinic Syndrome
  - Physostigmine can safely and effectively ameliorate the agitated delirium associated with the central anticholinergic syndrome

MANAGEMENT

- Enhanced Elimination
  - no pharmacologic rationale to support the use of multiple-dose charcoal or manipulation of urinary pH to increase the clearance of antipsychotics
  - Because most antipsychotics have large volumes of distribution and extensive protein binding, neither hemodialysis nor hemoperfusion are expected to significantly increase their clearance

J Clin Psychopharmacol. 2007 Dec;27(6):667-71.

Hemoperfusion in the treatment of acute clozapine intoxication in China.

He JL, Xiang YT, Li WB, Cai ZJ, Ungvari GS.

- In a retrospective chart review, the notes of 47 patients who attempted suicide by ingesting large amounts of clozapine and were treated at the only psychiatric emergency service in Beijing were analyzed. Of the 20 unconscious patients with plasma clozapine concentrations of more than 2000 ng/mL, 14 received a combination of HP and symptomatic treatment, whereas the other 6 and the remaining 27 patients received only symptomatic treatment.
- One patient died of pulmonary edema and subsequent heart failure, but the rest of the patients recovered without any sequelae. Patients who received HP regained consciousness significantly faster than their counterparts with the same level of clozapine plasma concentration (>2000 ng/mL) who did not receive HP.

CONCLUSIONS:

- **A combination of HP and symptomatic treatment is the best therapeutic option when plasma clozapine concentration is high.**