

# Clozapine-Induced Fever

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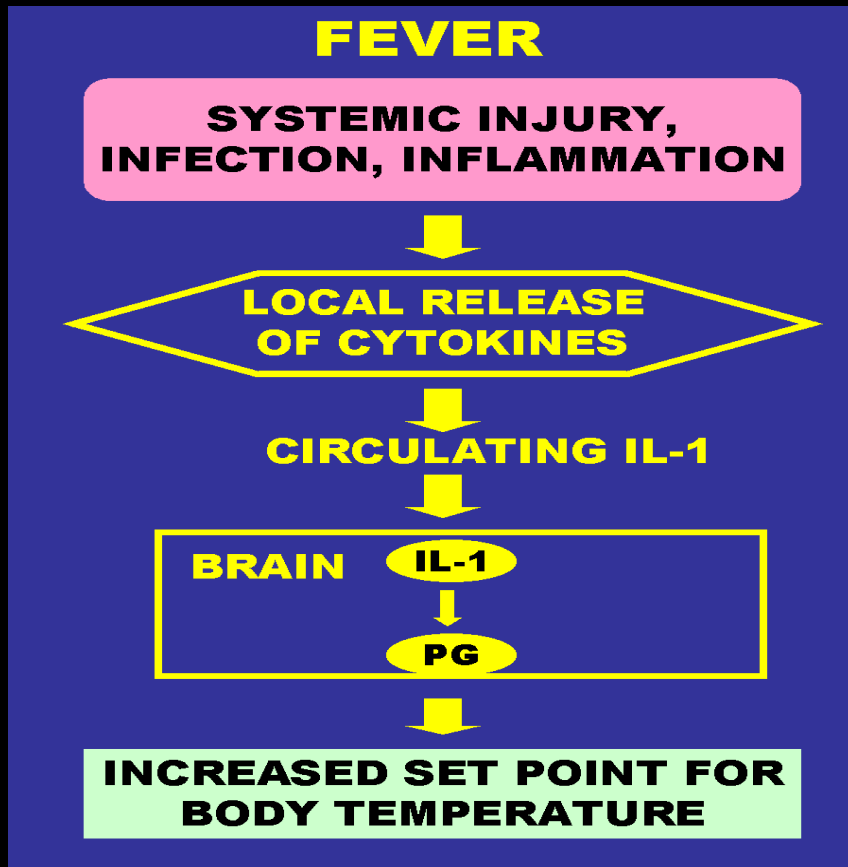
**Brooklyn, New York**

# Regulation of Body Temperature

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- Heat absorption or production  $>$  heat loss  
     rise in temperature
- Normal response to temperature increases  
     vasodilation and diaphoresis
- Homeostatic mechanisms control balance between heat production and loss
- Introduction of exogenous pyrogens or increase in endogenous pyrogens resets thermoregulatory process

# Mechanism of Fever



# Drugs Implicated in Fever

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- Interferon
- Amphotericin B
- Gentamicin
- Erythromycin
- Vancomycin
- Cephalosporins
- Penicillins
- Chemotherapeutic agents
- Opioids
- Alcohol
- Barbiturates
- Phenothiazines
- TCA/SSRI
- Amphetamine toxicity
- **Antipsychotics**
- Cardiovascular drugs
- Anticonvulsants

# Drug-induced Fever: Mechanisms


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- Direct/indirect pyrogenic effect by causing inflammation or damage
- Pyrogen release as part of pharmacology
- Alteration of thermoregulation via central, peripheral, metabolic means
- Hypersensitivity reactions
- Immunosuppression
- Idiosyncratic reactions

# Drugs/Reactions Leading to Fever




**Ecstasy** - MDMA and similar stimulants **Class A**  
E's - Doves



Found in a variety of forms and colours

**Amphetamines** **Class B**  
Speed - Uppers - Sweets - Whizz - Sulph



**CAUTION**

**CHEMOTHERAPY MATERIAL**

TRANSPORT BAG       WASTE BAG

WRITE -- ON PLACES

NAME: \_\_\_\_\_

PREPARED BY: \_\_\_\_\_

**AFTER USE, DISPOSE OF IN ACCORDANCE WITH ESTABLISHED PROCEDURES**

# Clozapine (Clozaril<sup>®</sup>): Introduction

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- First atypical antipsychotic approved for the treatment of schizophrenia (1990)
- Exhibits superior efficacy over typical antipsychotics and has minimal extra pyramidal symptoms (EPS)
- *Indicated for use in schizophrenic patients who are refractory to standard drug treatment*

# Clozapine (Clozaril<sup>®</sup>): Adverse Effects

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- Sialorrhea (75-85%)
- Drowsiness (39%)
- Orthostatic hypotension (18-33%)
- Weight gain (>30%)
- Tachycardia (25%)
- Dizziness (19%)
- Constipation (>5%)
- **Fever (>5%)**
- Seizures (3.5 – 5%)
- Agranulocytosis (1 -2%)
- Myocarditis (<1%)
- Neuroleptic malignant syndrome (NMS) (?)

# Clozapine-induced Fever

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- Temperature elevations above 104°F not been noted
- **Incidence:** > 5%
- **Onset:** typically 2 weeks into treatment with low doses of clozapine
- **Duration:** 2.5 days with constitutional symptoms, neutrophilia and increased erythrocyte sedimentation rate
- **Characteristics:** benign, transient, self-limiting; recovery with symptomatic treatment

# Case Report

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- Case of clozapine-induced fever without NMS with positive temporal relationship
- 51 y/o WM (5'9", 96.9 kg; CrCl 87 ml/min) admitted to geriatric psychiatry unit due to severe agitation and aggressive behavior
- CC: actively delusional, abusive to nursing staff, screaming, and responding to internal stimuli
- PMH: mental retardation, hypertension, urinary incontinence, and urethral strictures

# Case Report

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- Medications on admission
  - Olanzapine (Zyprexa<sup>®</sup>) 40 mg/d
  - Divalproex (Depakote<sup>®</sup>) 2000 mg qhs
  - Haloperidol (Haldol<sup>®</sup>) 5 mg am and hs
  - Clonazepam (Klonopin<sup>®</sup>) 2 mg tid
  - Fluvoxamine (Luvox<sup>®</sup>) 50 mg qd
  - Docusate sodium (Colace<sup>®</sup>) 300 mg qd
- VPA level upon admission = 74.6 mcg/ml
- Baseline CBC, chemistry, liver enzyme tests, thyroid function tests within normal limits

# Case Report

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- Prior antipsychotic trial failure
  - Quetiapine (Seroquel<sup>®</sup>): minimal response
  - Ziprasidone (Geodon<sup>®</sup>): QT – prolongation
  - Olanzapine (Zyprexa<sup>®</sup>): minimal response
- Day 20: Start clozapine 12.5 mg am & hs
- Day 23: Patient had a fall and eye laceration (placed on topical & systemic antibiotics)

# Case Report

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- Day 33: Patient developed cellulitis in right leg (placed on topical & systemic antibiotics)
- Day 35: Clozapine titrated to 100 mg am & hs



Patient developed fever of 100.4°F

Day	Event	Antibiotic	Temp (°F)	WBC/ Neutrophil
Day 33	Eye laceration	Clindamycin 450 mg PO q8h		7.8/ (58.9%)
Day 35			100.4	
Day 37		Clindamycin d/c	100.8	8.0/ (62.0%)
Day 38	Cellulitis rt. leg	Vancomycin 1 g IV q12h	99.8	9.0/ (65.9%)
Day 41		↑ Vancomycin to 1.5 g IV q12h	99.9	
Day 43	RLL pneumonia	Azithromycin 500 mg PO q24h	101	
Day 46	Clozapine d/c		100.6	
Day 47		Vancomycin d/c	98.6	
Day 50		Azithromycin d/c	98	

# Case Report

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- Day 40: patient experienced lethargy, sialorrhea, diaphoresis, CK = 113 IU/L
- Day 35 – 46: fever continued despite antibiotics and acetaminophen w/o leukocytosis or neutrophilia
- Day 46: temporal relationship with clozapine suspected and clozapine was discontinued
- Day 47: fever dissipated; vancomycin and azithromycin

# Mechanisms of Clozapine-induced Fever

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- Inhibition of serotonergic, noradrenergic, and cholinergic systems
- Impaired humoral and cell-mediated immunity
- Increases in plasma levels of soluble interleukin-2 receptors
- Excessive release of tumor necrosis factor- $\alpha$

# Clozapine-associated Fever

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- Common, but rarely associated with NMS
- Presentation of NMS due to clozapine may be atypical
  - Fever and rigidity less likely to occur
  - Elevations in WBC and CK tend to be mild (<1000 IU/L)
  - Diaphoresis may be more prominent
- Lack of response to multiple antibiotics

# Discussion

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- *Possible* correlation between drug and effect (Naranjo algorithm score: 4)
- Fever not associated with NMS evidenced by an unremarkable physical exam, normal CK levels, and a positive dechallenge
- Patient did not have agranulocytosis → WBC  $\geq 4.2$  cells/mm<sup>3</sup>
- Patient started on aripiprazole (Abilify®) 15 mg qd
- Patient improved in psychotic symptoms with no further adverse effects over next 8 days

# Conclusion

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- Fever is a side effect of clozapine
- Fever should not be a deterrent to treating with clozapine
- NMS and agranulocytosis must be considered due to potential harmful consequences
- In our patient, a lack of response to clozapine and unremitting fever constituted the rationale behind the dechallenge
- Clinicians should be cognizant of this adverse reaction and take adequate measures to modify treatment when necessary