


RESIDENT VIGNETTE

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HAVE A HEART: WIELDING CLOZAPINE

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HPI

- ▶ 24-year-old Korean-American male admitted from MHRC for sudden change in behavior
- ▶ Recent threats to group home staff
- ▶ Punched a peer w/o provocation
- ▶ Paranoid that staff and patients were looking at him sexually
- ▶ “I’m the smartest man in the world” & “I’m the most attractive man in the world”
- ▶ Extremely isolative, pacing, poor grooming, delusional

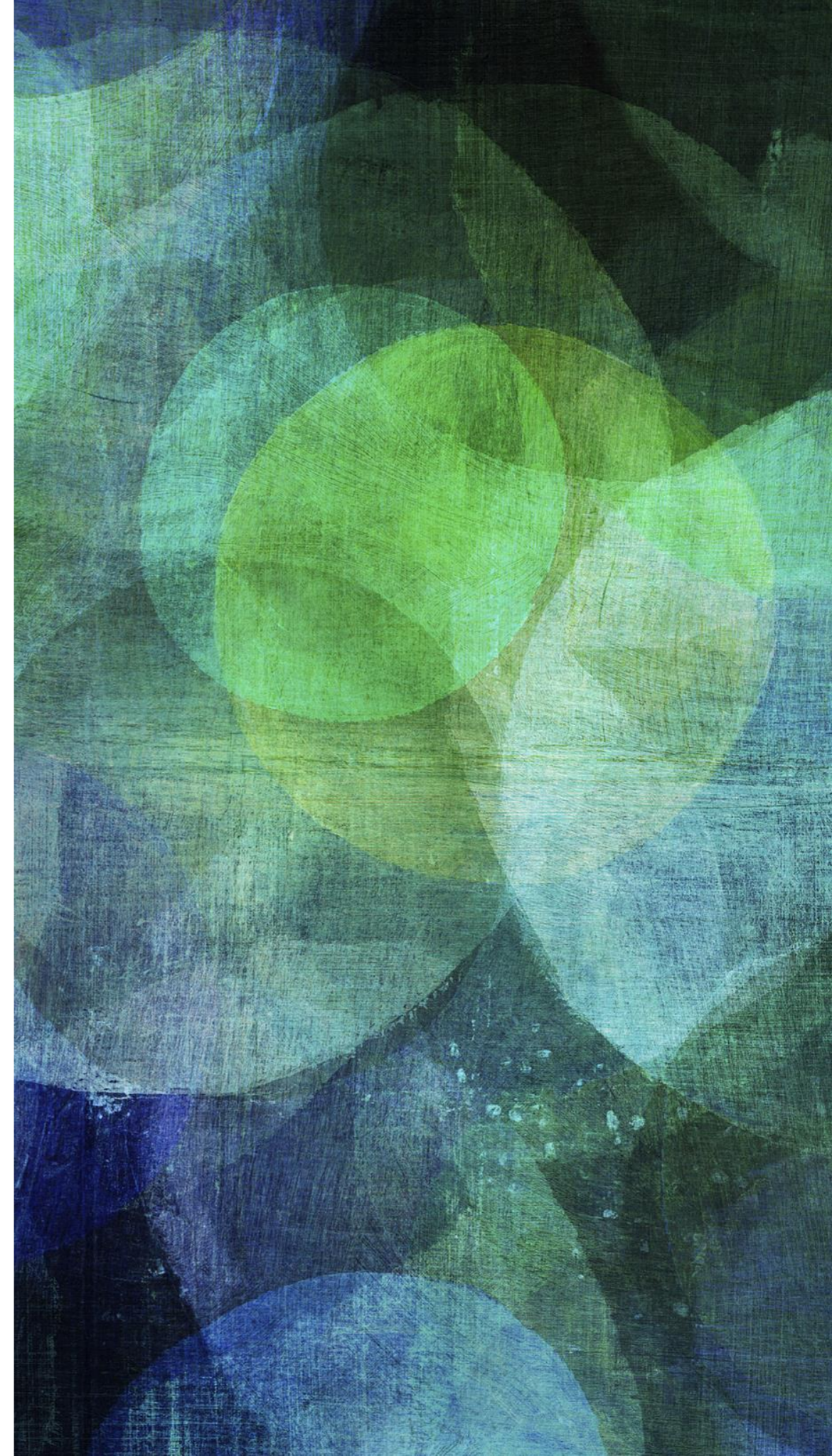
PAST PSYCHIATRIC HISTORY

- ▶ First psychiatric care at age 21 during senior year at prestigious college (sociology major)
- ▶ H/o of one suicide attempt
- ▶ 5 previous psychiatric admissions
- ▶ Mother and older sister placed restraining order
 - ▶ He reportedly tried to choke mother, “hog-tied” sister
- ▶ Previous trials of olanzapine, paliperidone and aripiprazole
- ▶ Diagnosis of schizoaffective d/o

- ▶ Lithium carbonate 1200mg HS
- ▶ Quetiapine 300mg HS
- ▶ Propranolol 10mg BID
- ▶ Clonazepam 2mg HS (and QD PRN)
- ▶ Recently taken off aripiprazole 30mg HS (cheeking suspected)
- ▶ TSH 2.02
- ▶ UDS negative
- ▶ Lithium level 0.9 mEq/L

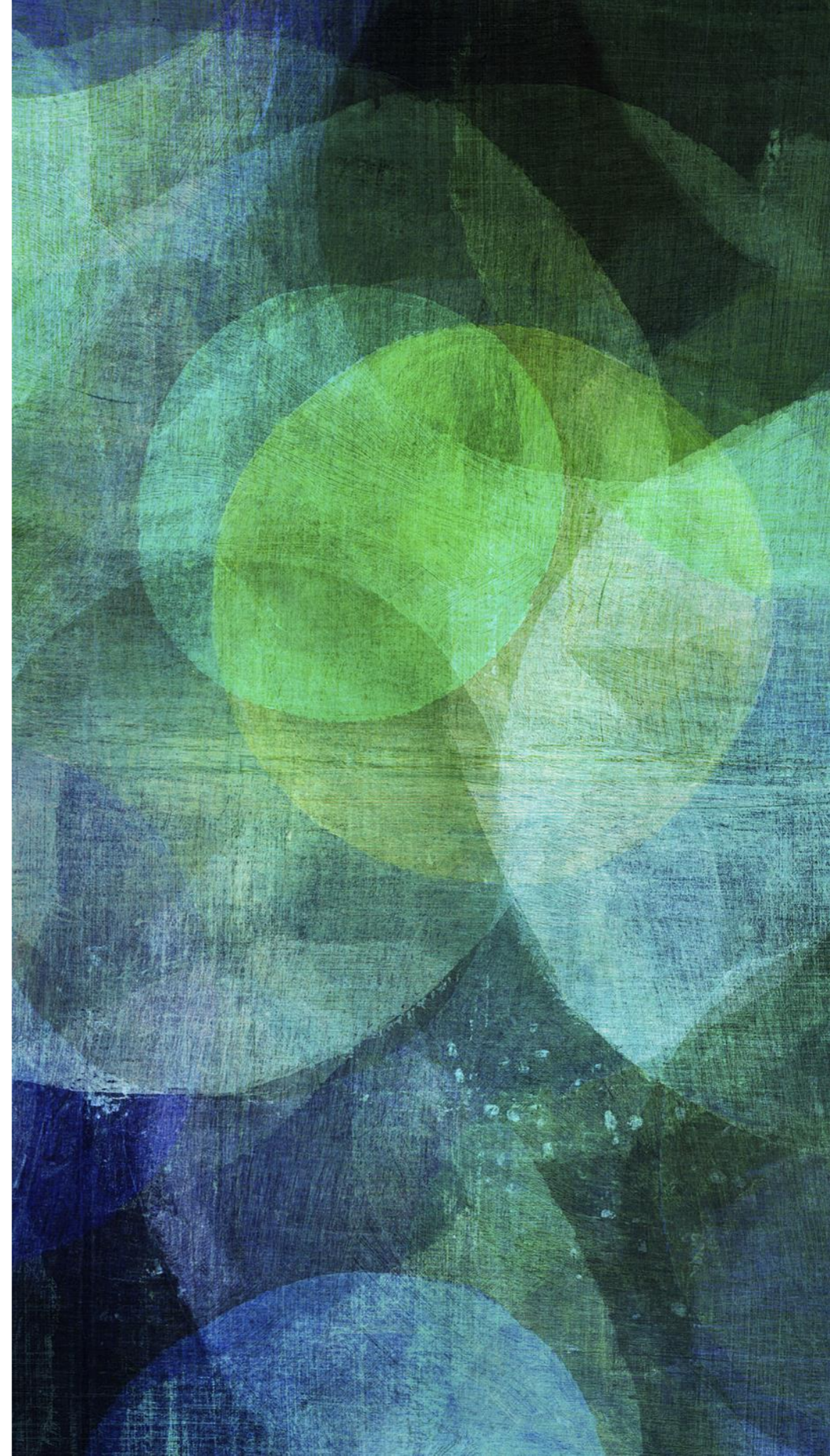
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ADMIT MEDS/LABS



- ▶ Started on clozapine and fluvoxamine
- ▶ Baseline CBC, CRP, troponins and EKG
- ▶ Reached goal of clozapine 200mg and 50mg fluvoxamine
- ▶ Sedated, but delusions and hypersexuality less overt

COURSE





CLOZAPINE: ADVERSE

..... EFFECTS

➤ Serious

- Agranulocytosis, neutropenia, seizure, myocarditis, paralytic ileus

➤ Common

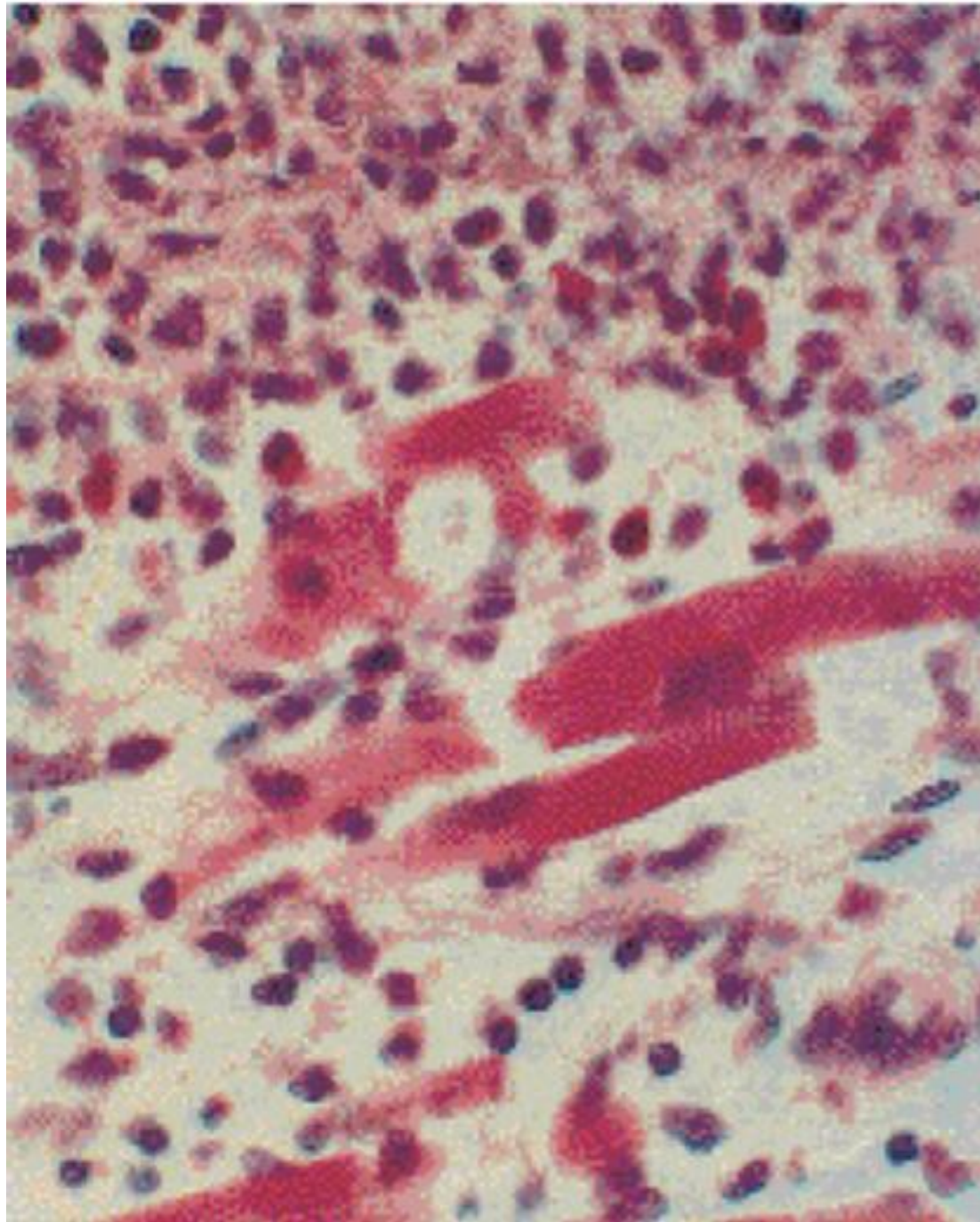
- Sedation, orthostasis, tachycardia, constipation, sialorrhea, urinary incontinence, weight gain and metabolic derangements

➤ Incidence/Mortality:

- Myocarditis (first 2 months): 0.2 to 3% / ~25% fatal
- Agranulocytosis: ~0.8%/ Monitoring has nearly eliminated

COURSE, CONTINUED

- ▶ Around Week 3 of tx, CRP reached 3 mg/dL (=30mg/L)
- ▶ More withdrawn, lethargic
- ▶ Afebrile; HR 100s-110s
- ▶ Endorsed CP & SOB
- ▶ WBCs to 15 w/o eosinophilia
- ▶ EKG changes
 - ▶ Increased PR interval and nonspecific ST-segment changes
- ▶ Week 3 TTE showed mildly decreased EF vs. low-normal, as well as enlarged RV (no baseline)
- ▶ Pt tapered off clozapine and switched to paliperidone



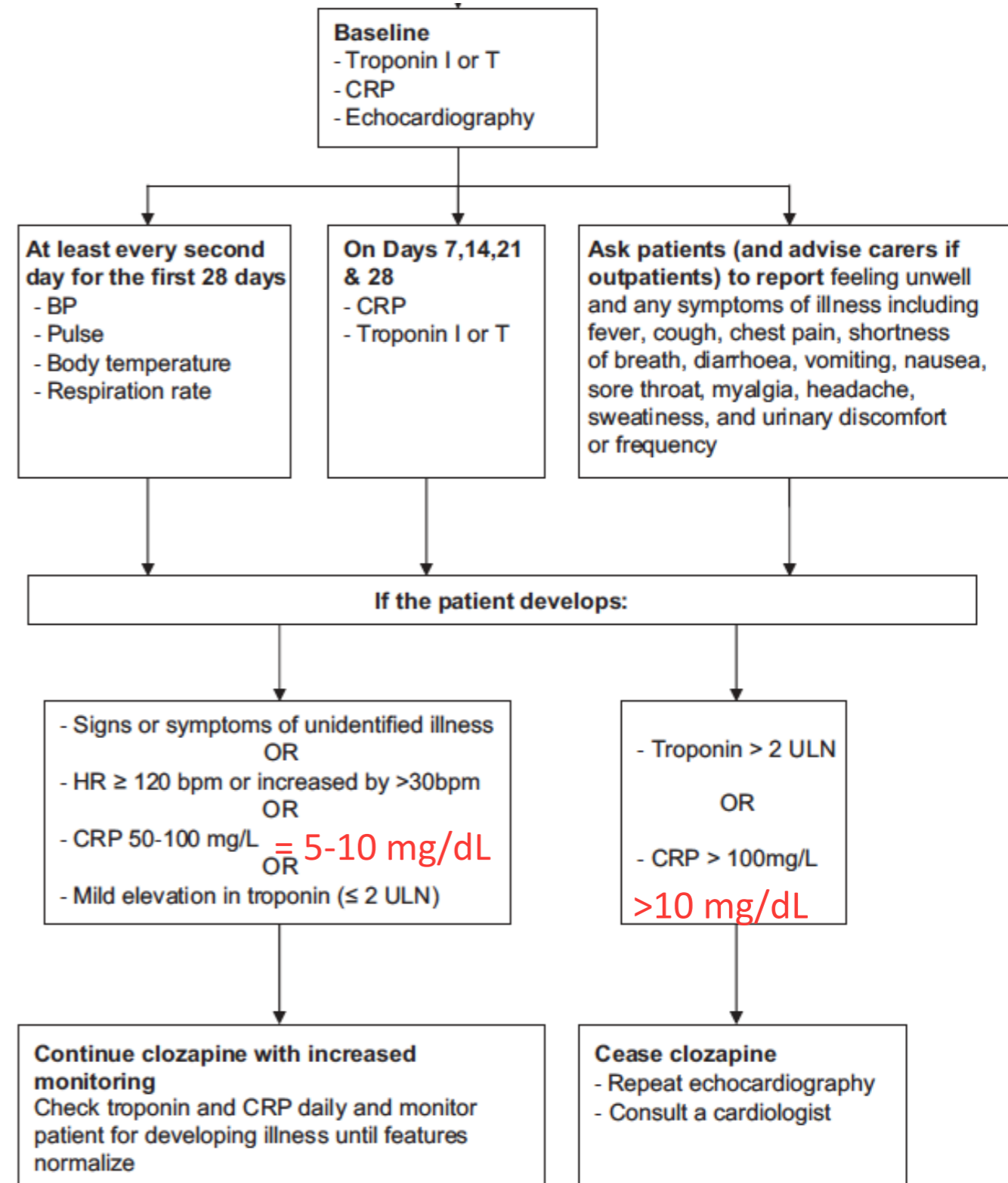
CLOZAPINE & MYOCARDITIS

- 23 cases
- 10-21 days from first dose to clinical presentation/death
- Suggest IgE-mediated hypersensitivity (Type I)
- Estimate 5-fold increased risk

Myocytolysis and necrosis w/ florid infiltrate of lymphocytes, neutrophils & eosinophils

MYOCARDITIS MONITORING

- 75 cases & 94 controls
- Week 3 mode for myocarditis
- Propose baseline echo
- Propose CRP+Trop at baseline & weekly x4 weeks
- Propose D/C threshold of Trop > 2xULN & CRP >10mg/dL



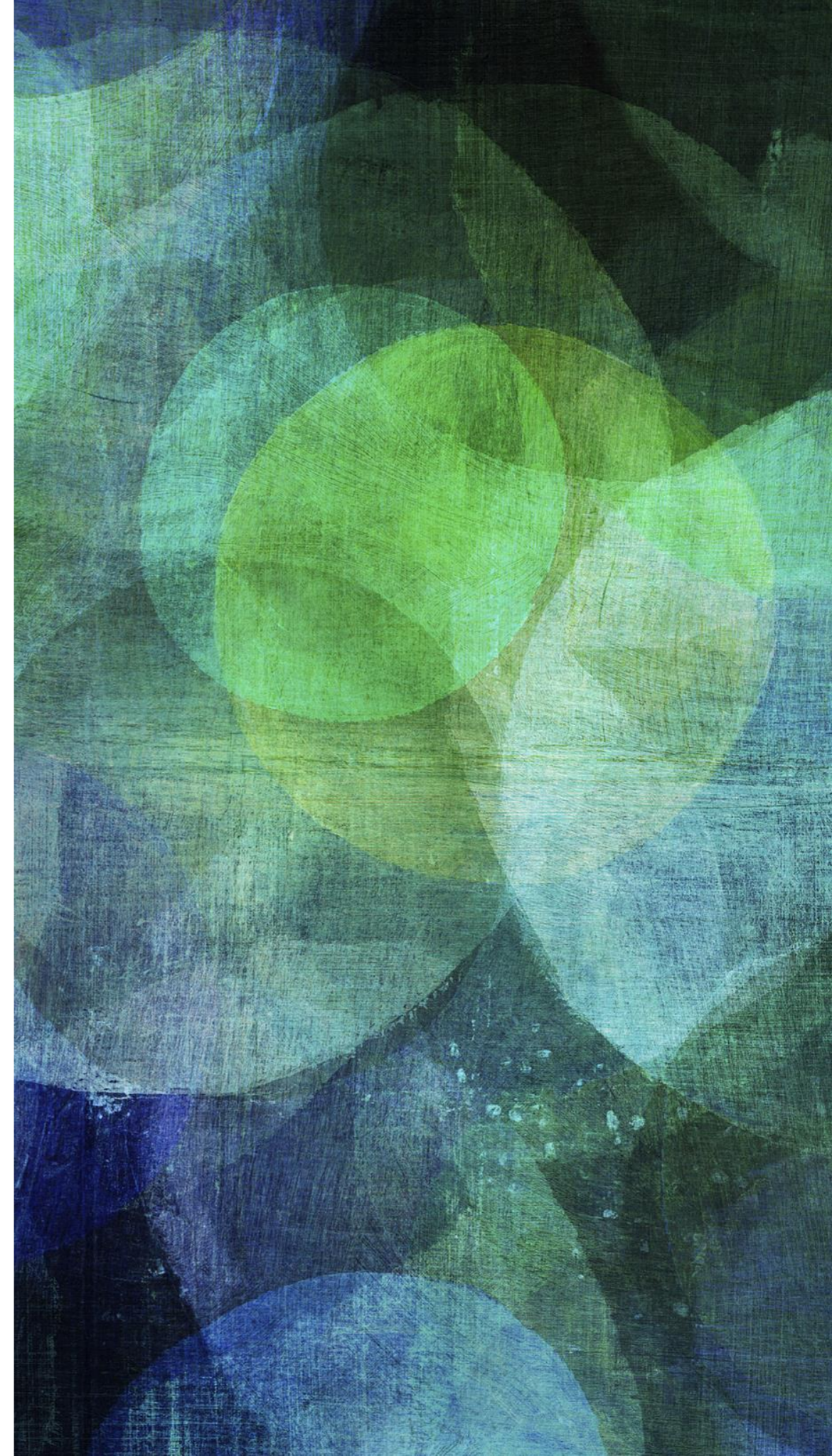
TAKE-AWAYS

- ▶ Myocarditis/cardiomyopathy may be as common as agranulocytosis in clozapine therapy
- ▶ Vast majority within 2 months, usually in Week 3
- ▶ Likely IgE-mediated hypersensitivity; however, eosinophilia not a reliable early indicator
- ▶ Reasonable monitoring:
 - ▶ Baseline EKG, troponins, CRP & echo
 - ▶ VS every other day for first month
 - ▶ Weekly troponins and CRP for first month
 - ▶ ↑'d Trops <2x ULN/CRP 5-10mg/dL → Intensify monitoring
 - ▶ ↑'d Trops >2x ULN/CRP >10mg/dL → STOP: Cardiology & Echo

- ▶ Contact made with sister
- ▶ Sister and mother paid for Korean therapist
- ▶ Pt accepted therapist from his community
- ▶ Maintained on paliperidone LAI
- ▶ No incidents of violence
- ▶ Transferred back to county MHRC
- ▶ Family preparing to accept him back home

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COURSE TO PRESENT



SOURCES

- ▶ Cook SC et al. Clozapine-induced myocarditis: Prevention and considerations in rechallenge. *Psychosomatics* (2015) 56:685-690
- ▶ Kilian JG et al. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* (1999) 354:1841-45
- ▶ Leucht S et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* (2013) 382:951-62
- ▶ Polcwiartek C and Nielsen J. The clinical potentials of adjunctive fluvoxamine to clozapine treatment: a systematic review. *Psychopharmacology* (2016) 233:741-750
- ▶ Ronaldson KJ et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Australian and New Zealand Journal of Psychiatry* (2011) 45:458-465.



A WORD: FLUVOXAMINE + CLOZAPINE

- ▶ ~70% variation in clozapine clearance due to CYP1A2 activity (minor 2D6, 3A4)
- ▶ Fluvoxamine strongly inhibits CYP1A2
- ▶ Shifts ratio of cloz:norcloz in favor of clozapine
 - ▶ 50mg fluvoxamine increases clozapine by ~120% and reduces norclozapine to as low as 24% of clozapine levels
- ▶ Possibly due to ↓ing norclozapine's 5HT_{2c} stimulation, causing ↓'d hunger, fluvoxamine decreases likelihood of metabolic effects
- ▶ However, clozapine more potent alpha-1 and histamine blocker
 - ▶ Increases likelihood of orthostasis and sedation

CHOOSING CLOZAPINE

- ▶ Meta-analysis of 212 trials, N = 43,049
- ▶ No industry funding
- ▶ “Our findings challenge the straightforward classification of antipsychotics into 1st- and 2nd-generation groupings.”
- ▶ Propose hierarchies in 7 major domains:
 - ▶ Including “overall change in symptoms”

CHOOSING CLOZAPINE

- ▶ Effective in treatment-resistant cases
- ▶ Effective in individuals with self-harming bx
- ▶ ↓ risk movement abnormalities

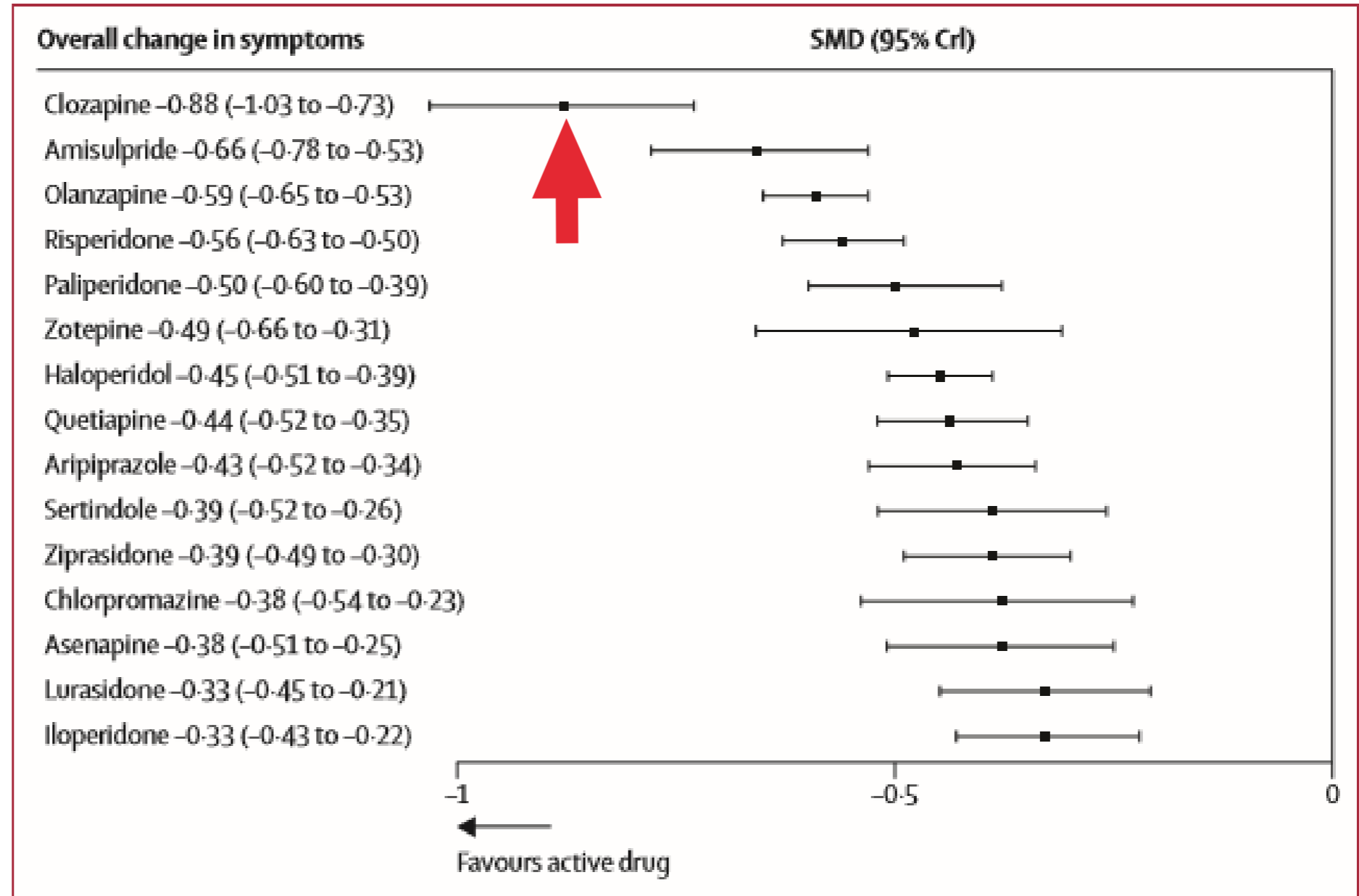


Figure 3: Forest plot for efficacy of antipsychotics drugs compared with placebo
Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix p 98).
SMD=standardised mean difference. CrI=credible interval.