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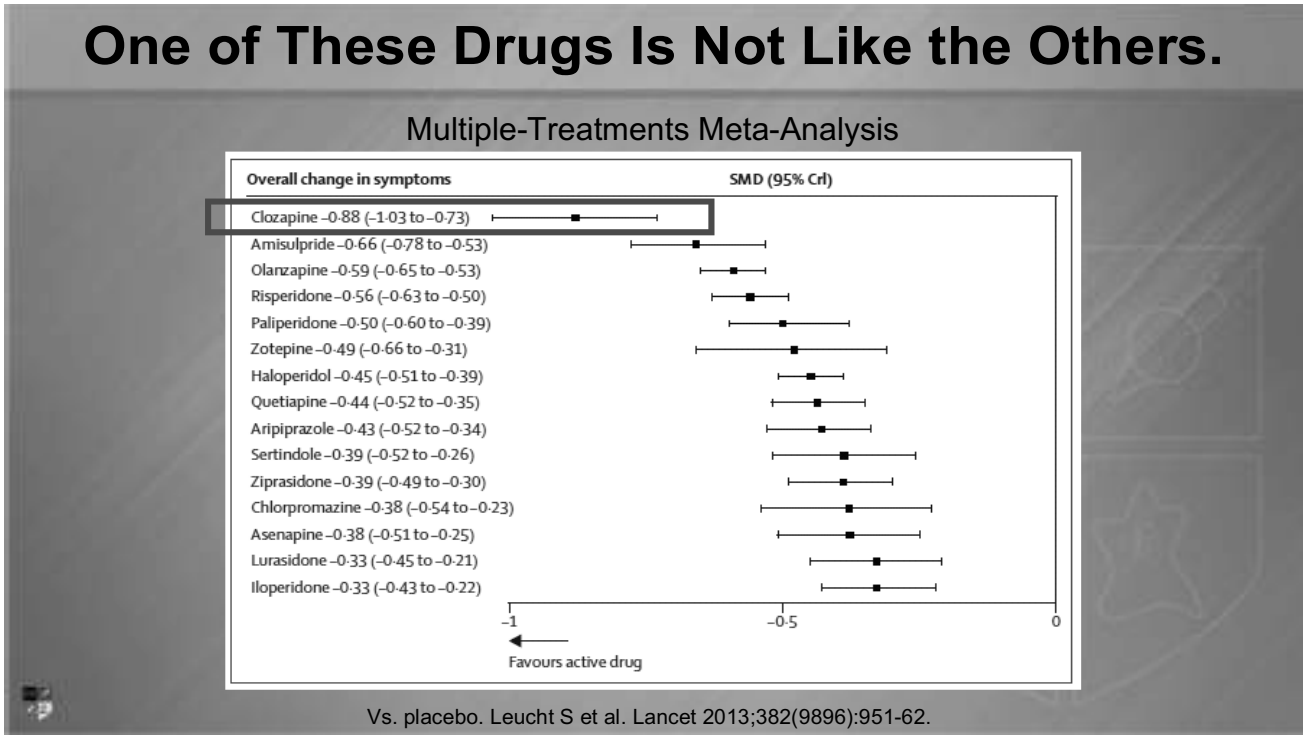
Second Generation Atypical Antipsychotic (SGA) Mood Stabilizers:
Clozaril

- Generic name is clozapine. Introduced 1989.
- FDA-approved for schizophrenia in adults, especially treatment-resistant schizophrenia; some evidence of efficacy in pediatric schizophrenia. May be useful in bipolar disorder, aggression. FDA-approved for the treatment of recurrent suicidal behavior in schizoaffective and schizophrenic patients (suicide completion rates have been noted to be 26-80% reduced from that of the general schizophrenic population). May be helpful in substance abuse, tardive dyskinesia, and borderline personality disorder.
- Evidence



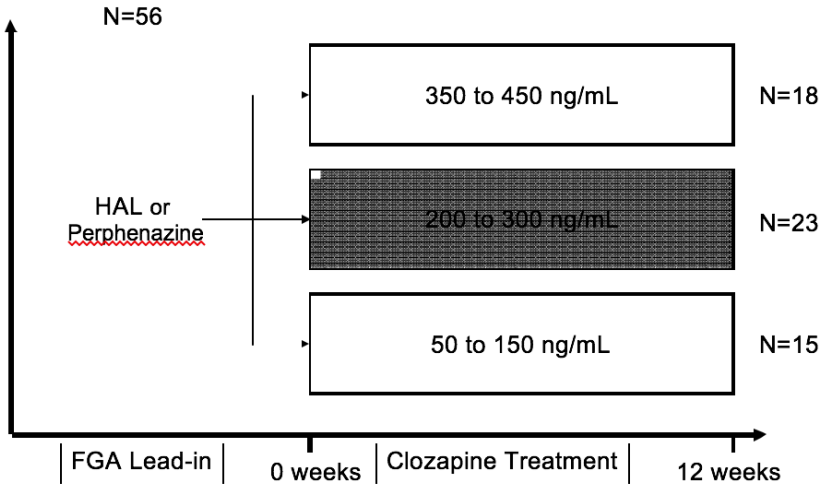
Vs. placebo. Leucht S et al. Lancet 2013;382(9896):951-62.

Potential Advantages of Clozapine

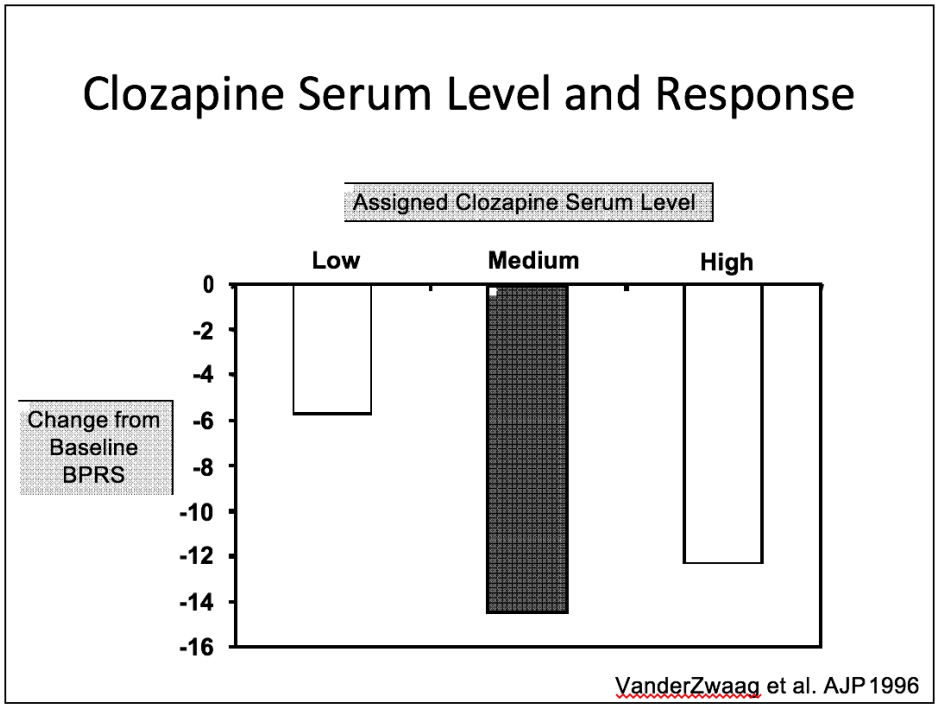
- Superior efficacy for
  - Psychotic symptoms
  - Treatment-resistant psychosis
  - Aggression and violence
  - Reducing suicide
- Low/no extrapyramidal side effects
- Low/no hyperprolactinemia
- Low tardive dyskinesia; can even improve tardive dyskinesia
- Can be used in Lewy body dementia or Parkinson's psychosis

Stahl SM. Stahl's essential psychopharmacology: the prescriber's guide. 6th edition. New York, NY: Cambridge University Press; 2017.

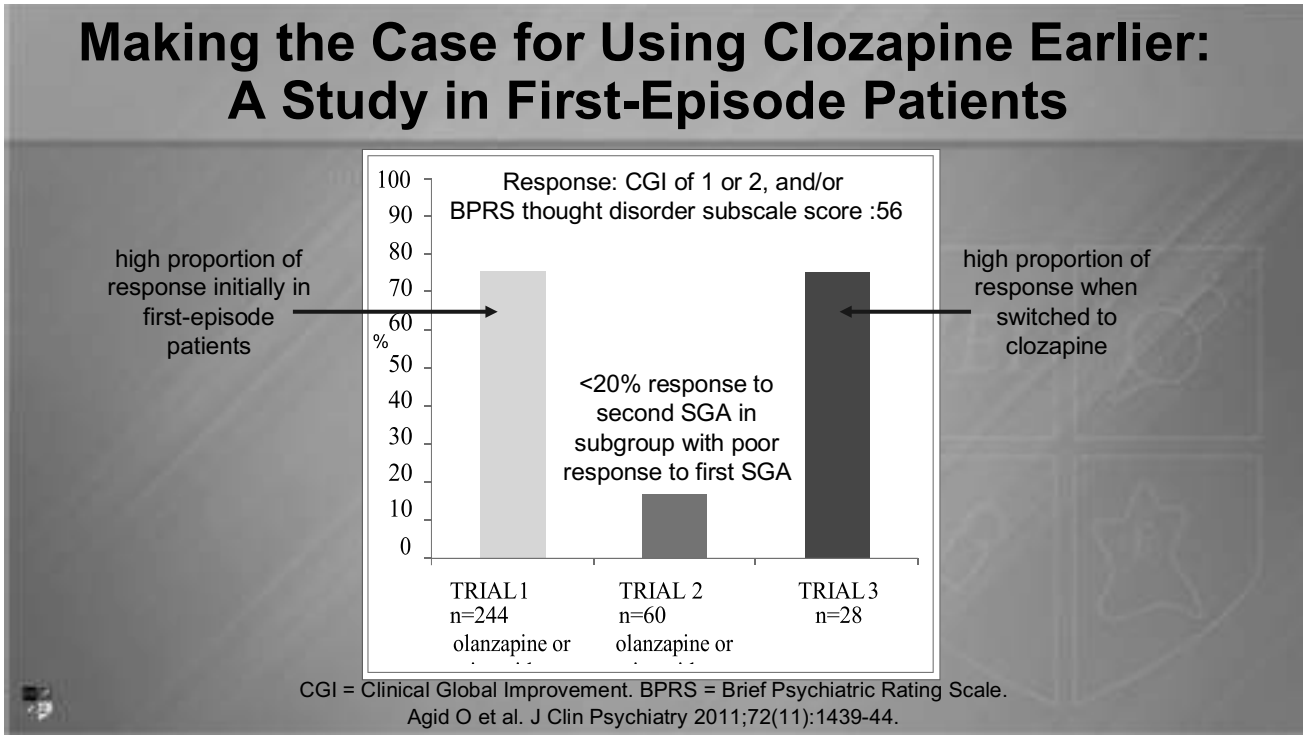
Prospective, randomized trial of 3 ranges of clozapine blood levels



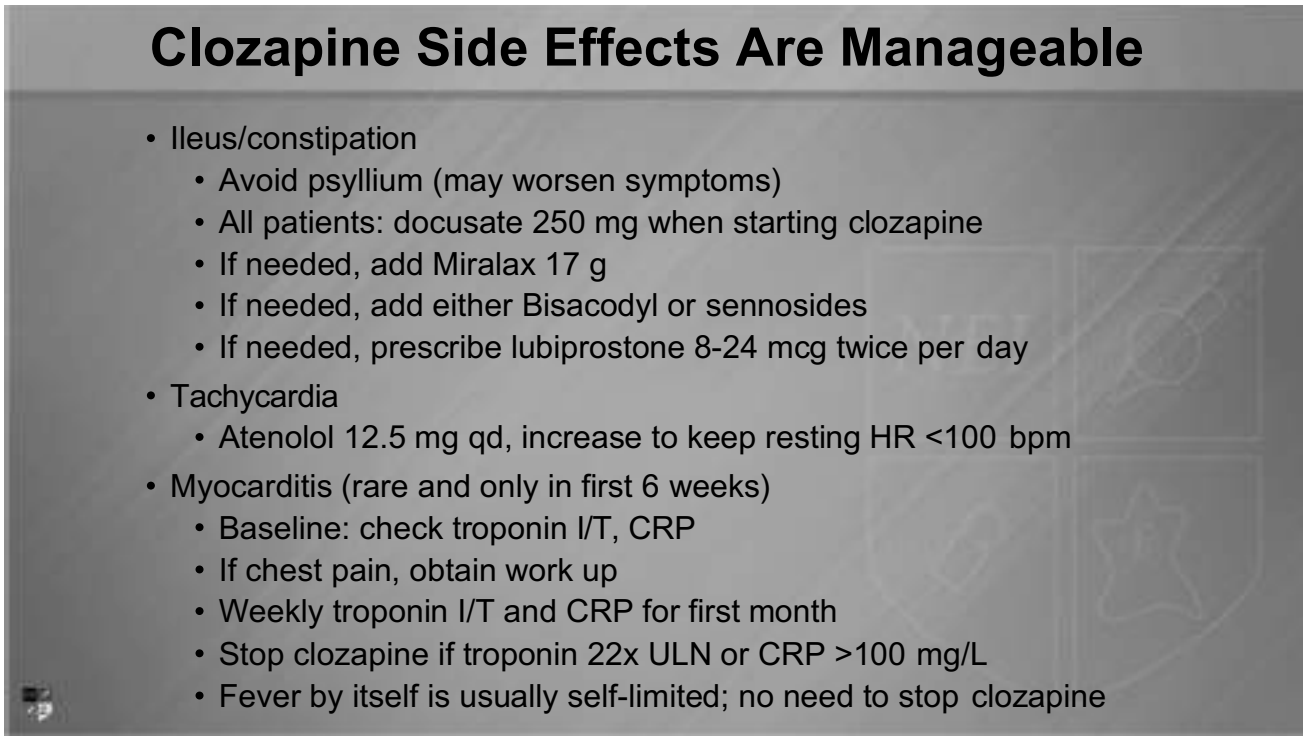
VanderZwaag et al., AJP 1996



- Wimberly et al, 2017
  - Treatment-resistant schizophrenia and clozapine; association with (reduced) mortality and self-harm
    - 2370 folks with treatment-resistant schizophrenia (TRS), 1996-2013
    - Rate of all-cause mortality 1.88X higher for folks with TRS not taking clozapine than those taking clozapine
      - 2.5X higher for folks with TRS not taking ANY medication
      - 1.45X higher for folks with TRS taking meds other than clozapine (this was non-significant, given the range of risk from 0.86X (less) to 2.45X (more))
    - Excess mortality was observed in the year after clozapine discontinuation
    - Rate of self-harm was 1.36X higher for nonclozapine antipsychotics than for clozapine
- Stroup et al, 2016
  - Initiating treatment with Clozapine vs. other standard antipsychotic for adults with schizophrenia; initiating with clozapine associated with significant
    - Reduced rate of psychiatric hospital admission (hazard ratio of 0.78)
    - Reduced rate of first antipsychotic discontinuation (hazard ratio of 0.60)
    - Reduced rate of use of additional antipsychotic medication (hazard ratio of 0.76)
    - Increased incidence of diabetes (2.8% vs. 1.4% for standard antipsychotic for a hazard ratio of 1.63)
    - Increase rate of hyperlipidemia (12.9% vs. 8.5% for standard antipsychotic for a hazard ratio of 1.4)
    - Increased rate of intestinal obstruction (0.9% vs. 0.3% for standard antipsychotic for a hazard ratio of 2.5)



  - Chang et al, 2006
    - Long-term clozapine add-on therapy reduced rehospitalization rates in bipolar disorder in adults by 90.2%
  - Kant, 2004:
    - Clozapine in teens (with bipolar disorder, IED, PTSD; chart review, mean dose 102
  - Masi et al, 2002:
    - Severe, treatment resistant mania or mixed mania in teens, 10 total, mean dose 142.5 (75-300 mg/day)
    - All 10 responded
    - Mean weight gain 14 pounds (range 8-20)
- Evidence in youths with schizophrenia:
  - Kranzler, 2005:
    - 20 children, 8.5-18, with schizophrenia and aggression, mean dose 476 (range 350-600)
    - Positive efficacy
  - Kumra, 1996—21 youths (~14 yo), vs. Haldol, Clozapine superior, 1/3 stopped due to side effects/risks
  - Remschmidt, 1994—36 adolescents with treatment resistant schizophrenia, duration ~154 days, ¾ with "some" improvement
- Mechanism
  - Potentiates NMDA glutamate transmission via glycine transporter type 1 blockade.
  - Other
- Effective dose range 300-600 mg/D with full range of 100-900 mg/d; increased risk of seizures at escalating doses.

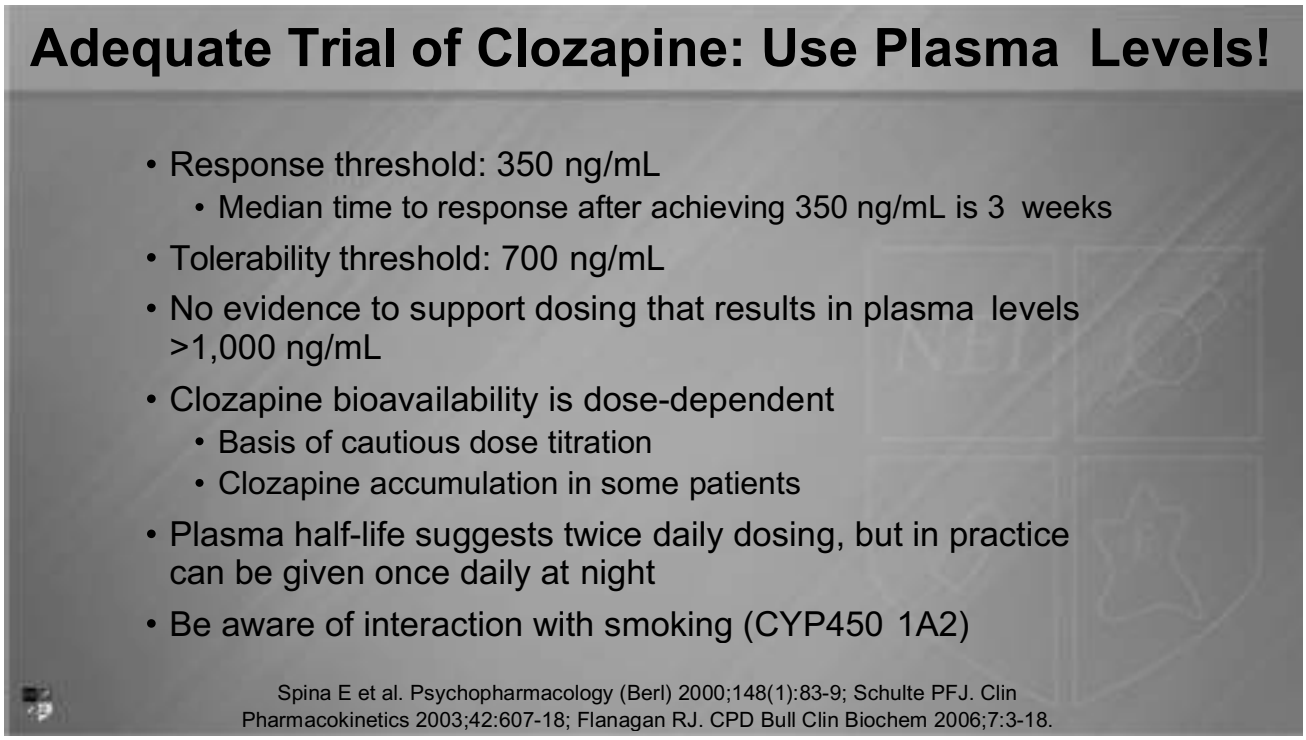


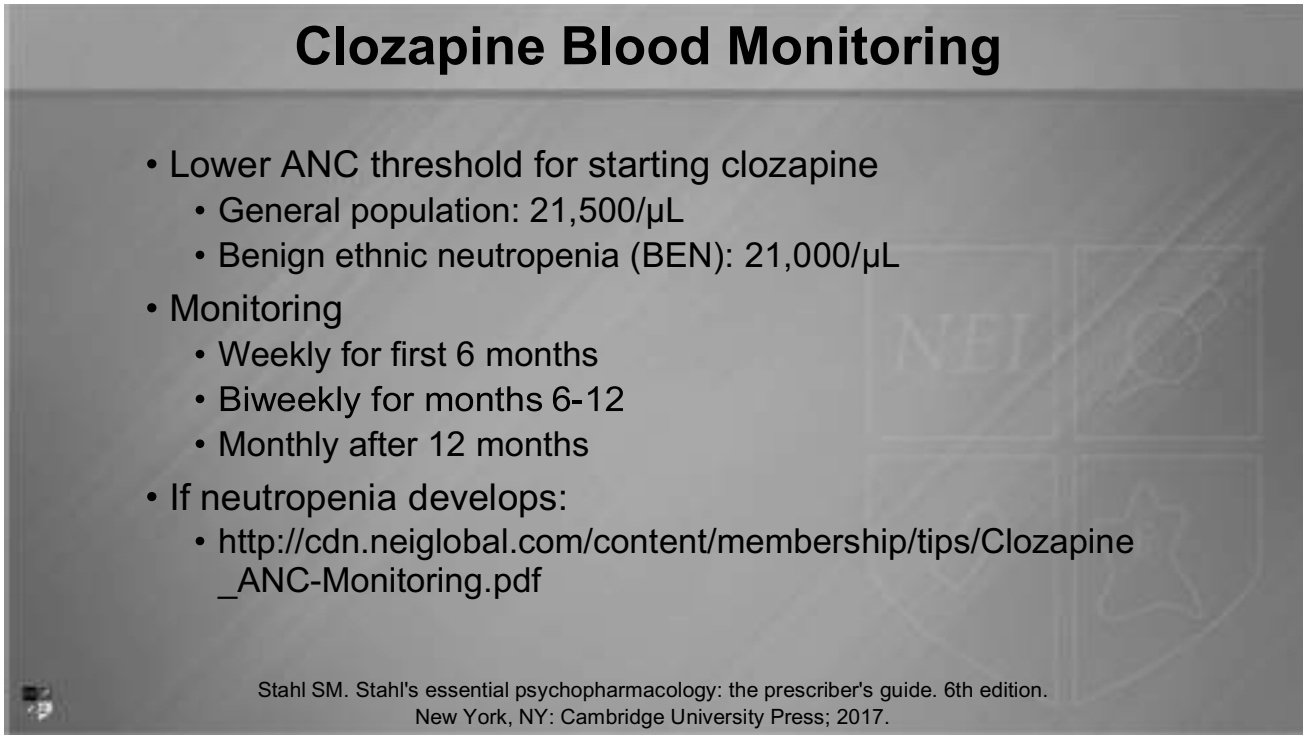
- Some of the side effects and risks include:
  - myocarditis (5-97 cases per 100,000 patient years; 2.8-32 fatalities per 100,000 patient years; mostly in 4-8 weeks)/cardiomyopathy; get troponin levels, ECG, echo
  - orthostatic hypotension, cardiac collapse, respiratory arrest (if off stop clozapine for 2 days or more, restart at 12.5 mg/D and increase very slowly to minimize risk of cardiac problems)
  - agranulocytosis (see below)
  - sedation
  - hypersalivation; clonidine or Seroquel (25-100 mg) can help.
  - weight gain—average ~11 pounds
  - glucose intolerance/diabetes
  - dose-dependent risk of seizures (15% of patients)
  - urinary incontinence; ddAVP may help
  - liver abnormalities
  - stuttering
  - dry mouth
  - constipation
  - drug-induced fevers (~100 degrees) can come and pass early in treatment
  - malignant hyperthymia—high temperature, fast heart rate/increased blood pressure, +/- muscle rigidity and CPK enzyme elevation; hospitalization required
  - low platelets
  - eosinophilia
  - increased platelets
  - increased wbc (exclude myocarditis, NMS, infection, agranulocytosis)
  - benign fever (exclude myocarditis, NMS, infection, agranulocytosis)
  - NMS
  - venous thromboembolism
  - constipation

- increased liver enzymes
- increased risk of seizures
- Bed wetting
- a number of other side effects and risks in multiple organ systems.

- Agranulocytosis:
  - "defined as an absolute neutrophil count (ANC) of less than 500/mm ^{3}, has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with CLOZARIL® (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL® (clozapine) induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL® (clozapine) induced agranulocytosis, despite strict adherence to the required frequency of monitoring. In the U.S., under a weekly WBC monitoring system with CLOZARIL® (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal. During this period 150, 409 patients received CLOZARIL® (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among Clozaril® (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3 per 1000 person-years. After six months, the weekly incidence of agranulocytosis declines still further, however, never reaches zero."
  - **The death rate for the hematologic side effects from clozapine appears to be 1/10,000, while the estimated death rate in high risk schizophrenic patients for suicide appears to be 1 in 4-5 over a 7-year period. The life time risk for suicide in all schizophrenic patients appears to be 1 in 8-12.**
  - Not dose-related. May be autoimmune.
  - Most (but not all) cases occur in the second through fourth months of treatment.
  - Lahdelma et al, 2012, Finland, 1982-2007
    - 10.3 of cases occurred after the second year
    - In some patients, occurred after 13, 14, and even 22 years of treatment
    -
  - Gerbino-Rosen, 2005: in children and adolescents, 1 year of treatment:
    - Low neutrophil count in 13%
    - Agranulocytosis in 0.6%
    - Cumulative probability of developing a hematological adverse event was 16.1% after one year of treatment
  - All patients taking Clozaril must be registered in one of three national registries.
    - Clozaril National Registry (Novartis): (800) 448-5938; www.clozarilregistry.com
    - Clozapine Patient Registry (Ivax): (800) 507-8334; www.clozapineregistry.com
    - Clozapine Prescription Access System (CPAS, Mylan): (800) 843-9915; www.mylan-clozapine.com
- Does not appear to cause tardive dyskinesia; can treat tardive dyskinesia.

- Comes in 25 and 100 mg tabs. Comes generic.
- Metabolized by 1A2, primarily, but also 2D6 and 3A4
- Half-life is 16 hours (elsewhere listed as 8 hours)
- Time to max is 1-4 hours
- Caution when combined with fluvoxamine, other 1A2 inhibitors, lithium, and, especially carbamazepine.





Clozapine White Blood Cell Monitoring

- Initiation
  - WBC must be 3500 or more
  - ANC must be 2000 or more
- Weekly wbc/diff for 6 months
- Every 2 weeks for 6 months
- Then every 4 weeks
- A single drop or cumulative drop of 3000 or more in wbc or 1500 or more in ANC
    - Repeat tests
    - Monitor as appropriate twice-weekly til values above 3500/2000

Benign Ethnic Neutropenia and Clozapine Use: A Systematic Review of the Evidence and Treatment Recommendations
Peter Manu, Nilofar Sarvaiya, Liliana M Rogozea, John M Kane, Christoph U Correll
Journal of Clinical Psychiatry 2016, 77 (7): e909-16

OBJECTIVE: To evaluate the epidemiology, pathobiology, and management of benign ethnic neutropenia and determine the extent to which these factors should influence measures designed to avoid clozapine-induced agranulocytosis.
DATA SOURCES: A structured MEDLINE search with no language limitation was performed from database inception until March 31, 2015, using the terms clozapine and benign ethnic neutropenia. Retrieved articles were cross-checked for additional relevant studies.
STUDY SELECTION: Included in the study were articles that reported on the prevalence, etiology, and complications of benign ethnic neutropenia and the hematologic outcome of clozapine treatment in patients with this condition.
DATA EXTRACTION: Study results that documented the epidemiology, pathobiology, and clozapine utilization in persons of African, Arabian, and Mediterranean descent with a neutrophil count in the 1,000-1,800/mm^3 range.
RESULTS: The search identified 342 publications. Forty-two articles described the epidemiology, pathobiology, and management of benign ethnic neutropenia. Of these, 12 articles described patients with benign ethnic neutropenia whose neutrophil count decreased during treatment with clozapine. Persons with benign ethnic neutropenia do not have signs of impaired phagocytosis, and the frequency, severity, and outcome of their infections are similar to those observed in the general population. These features suggest that a neutrophil count > 1,000/mm^3 is safe for initiating and/or resuming clozapine therapy.

CONCLUSIONS: The presence of benign ethnic neutropenia should not prevent treatment with clozapine. Patients with benign ethnic neutropenia who develop a clozapine-induced decrease in the neutrophil count, but have no evidence of infection or impaired phagocytosis, may resume clozapine as soon as they have > 1,000 neutrophils/mm^3.

Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders

Chi-Shin Wu, Sheng-Chang Wang, I-Jin Yeh, Shi-Kai Liu

Journal of Clinical Psychiatry 2016, 77 (5): e573-9

OBJECTIVE: To compare the risk of antipsychotic-related seizure (ARS) by identifying seizures first diagnosed within 12 months after starting new antipsychotics, using a 12-year total population health claims database from Taiwan.
METHODS: Seizure events were identified through emergency department visits or hospitalization with a diagnosis of convulsion (ICD-9-CM: 780.3) or epilepsy (ICD-9-CM: 345). Subjects had an ICD-9-CM diagnosis of schizophrenia, bipolar disorders, or major depressive disorders. Incidence rates of ARS were calculated by person-years of exposure. The ARS risk, adjusted for patient characteristics and medical conditions, of individual antipsychotics versus risperidone was examined by high-dimensional propensity score stratification analyses, followed by sensitivity analyses.
RESULTS: The overall 1-year incidence rate of ARS was 9.6 (95% CI, 8.8-10.4) per 1,000 person-years (550 ARS events among 288,397 new antipsychotic users). First-generation antipsychotics were marginally associated with a higher ARS risk than second-generation antipsychotics (adjusted hazard ratio [aHR] = 1.34; 95% CI, 0.99-1.81; P = .061). Most antipsychotics, first- or second-generation, had comparable ARS risks versus risperidone. Notably, clozapine (aHR = 3.06; 95% CI, 1.40-6.71), thioridazine (aHR = 2.90; 95% CI, 1.65-5.10), chlorprothixene (aHR = 2.60; 95% CI, 1.04-6.49), and haloperidol (aHR = 2.34; 95% CI, 1.48-3.71) had higher ARS risks than risperidone, whereas aripiprazole (aHR = 0.41; 95% CI, 0.17-1.00; P = .050) had a marginally lower ARS risk. Sensitivity analyses largely confirmed such findings.
CONCLUSIONS: Higher vigilance for ARS is warranted during use of clozapine, chlorprothixene, thioridazine, and haloperidol. The possible lower ARS risk associated with aripiprazole can be clinically significant but needs to be confirmed by larger-scale systematic studies. The comparative ARS risks of antipsychotics supplement empirical knowledge for making judicious choices in prescribing antipsychotics.

Clozapine and risperidone in moderately refractory schizophrenia: a 6-month randomized double-blind comparison

Nina R Schooler, Stephen R Marder, K N R Chengappa, Georgios Petrides, Donna Ames, William C Wirshing, Marjorie McMeniman, Robert W Baker, Haranath Parepally, Daniel Umbricht, John M Kane

Journal of Clinical Psychiatry 2016, 77 (5): 628-34

OBJECTIVE: Clozapine remains the only medication indicated for refractory schizophrenia. As new antipsychotic drugs become available, their efficacy compared to clozapine, particularly in moderately ill patients, is of great clinical interest. We compared risperidone, the first of these, to clozapine in partially responsive patients. Further, since participation of patients usually excluded from clinical trials is increasingly important, we broadened inclusion to a wider patient population.
METHODS: We compared clozapine (n = 53) to risperidone (n = 54) in a randomized, double-blind, 29-week trial in schizophrenia patients (diagnosed using DSM-IV) at 3 research outpatient clinics. Randomization was stratified by "narrow" or "broad" inclusion criteria. The study was conducted between December 1995 and October 1999. Time to treatment discontinuation for lack of efficacy and time to 20% improvement in the Brief Psychiatric Rating Scale psychotic symptom cluster were the primary outcome measures.
RESULTS: There were no differences in all-cause discontinuation; clozapine-treated participants were significantly less likely to discontinue for lack of efficacy (15%) than risperidone-treated participants (38%) (Wilcoxon $\chi(2)1 = 6.10$, P = .01). Clozapine resulted in significantly more global improvement ($F2,839 = 6.07$, $P < .01$) and asociality improvement ($F2,315 = 6.64$, $P < .01$) than risperidone. There was no difference in proportions meeting an a priori criterion of psychosis improvement (risperidone: 57%; clozapine: 71%). Significant adverse effect differences in salivation ($F1 = 4.05$, $P < .05$) ($F1 = 12.13$, $P < .001$), sweating ($F1 = 5.07$, $P < .05$), and tachycardia ($F1 = 6.51$, $P < .05$) favored risperidone.
CONCLUSIONS: Clozapine-treated partially responsive patients were less likely to discontinue treatment for lack of efficacy and improved more globally than those treated with risperidone, although psychotic symptoms did not differ. These findings suggest that clozapine should not be restricted to the most severely ill, treatment-refractory patients; it should be considered as an alternative for patients who have some response to other antipsychotics, but still experience troubling symptoms.

Strong Treatment Response and High Maintenance Rates of Clozapine in Childhood-Onset Schizophrenia

Lauren I Kasoff, Kwangmi Ahn, Peter Gochman, Diane D Broadnax, Judith L Rapoport

Journal of Child and Adolescent Psychopharmacology 2016, 26 (5): 428-35

OBJECTIVE: Childhood-onset schizophrenia (COS) is a rare but severe form of the disorder, which is often treatment refractory. Short-term studies have indicated a greater differential efficacy, evident through effect sizes, favoring clozapine over other agents in alleviating negative symptoms in COS patients compared with adult-onset patients (AOS). There have been no data for COS patients on long-term compliance with clozapine treatment. Therefore, we wanted to know, over a span of up to 24 years, how many of our COS cohort had remained on clozapine for at least 2 years. We review short-term treatment data and present updated long-term data on compliance and functioning for our patients.
METHODS: We present the results for long-term medication maintenance over a 24 year observation period for our cohort of 131 patients. Of this cohort, 91.6% (120) were available for follow-up information from either in-person or

telephone contact with the patient and/or family members. We defined clozapine compliance as ≥2 years receiving this medication and doing well.
RESULTS: We were able to contact 120 of the 131 patients. In spite of the additional cost and inconvenience of regular blood monitoring, 87 patients (72.5%, 87/120) adhered to long-term clozapine maintenance therapy with dosages ranging from 50 to 900mg, and a median dosage of 500mg. This rate exceeds the long-term clozapine maintenance rates reported for AOS patients.
CONCLUSIONS: Short-term data on differential efficacy and long-term maintenance data suggest a possibly greater efficacy of clozapine, relative to other antipsychotics, in COS than in AOS. Our overall findings indicate that very early-onset schizophrenic patients may be more responsive to clozapine. This extends other support for clozapine as an option in the treatment of early-onset schizophrenia.

Clozapine for Drug-Refractory Irritability in Individuals with Developmental Disability
Logan K Wink, Ismail Badran, Ernest V Pedapati, Rena Sorensen, Stacy C Benton, Mark C Johnson, Gregory Wissel, Craig A Erickson
Journal of Child and Adolescent Psychopharmacology 2016 March 17
OBJECTIVES: In this case series, we describe the acute clinical impact and tolerability of rapid titration of clozapine for treatment of refractory irritability in five hospitalized youth with developmental disability. We offer this descriptive report in an effort to expand the evidence base guiding treatment of refractory aggression in this population.
METHODS: Five youth with developmental disability and severe irritability were admitted to a 10-bed psychiatric crisis stabilization unit where they received thorough psychiatric and medical evaluation. Informed consent was obtained in each case, and each patient underwent rapid titration onto clozapine. Clozapine monitoring guidelines were followed for all patients throughout treatment, and clinical severity at baseline and improvement with treatment was measured by use of the Clinical Global Impressions-Severity scale (CGI-S) and the Clinical Global Impressions-Improvement scale (CGI-I).
RESULTS: One female and four males diagnosed with developmental disability and at least one other psychiatric diagnosis, mean age of 13.1±2.1 years, and mean CGI-S at baseline of 5.8, each received clozapine treatment by rapid titration. The mean therapeutic total daily dose of clozapine was 380±200mg. All patients demonstrated acute clinical improvement with the mean final CGI-I of 2.0, or "much improved."
CONCLUSION: These initial results support the potential utility of clozapine rapid titration for treatment of severe refractory irritability in youth with developmental disability. These patients tolerated clozapine treatment in the short term. Future studies are needed to thoroughly evaluate the long-term safety of clozapine treatment in this population.

Evaluation of the Safety of Clozapine Use in Patients With Benign Neutropenia
Charles M Richardson, Erica A Davis, Gopal R Vyas, Bethany A DiPaula, Robert P McMahon, Deanna L Kelly
Journal of Clinical Psychiatry 2016 October 11
OBJECTIVE: To determine if clozapine can be safely utilized in psychiatric patients with benign neutropenia.
METHODS: A single-center, retrospective chart review study of records from 2001 to 2014 was conducted in an inpatient psychiatric hospital. Patients included had benign neutropenia prior to receiving clozapine and received clozapine using modified monitoring guidelines. All available laboratory values for absolute neutrophil count (ANC) before initiation and during treatment were evaluated. The primary endpoint was difference in ANC after initiation of clozapine from before clozapine.
RESULTS: A total of 26 patients were reviewed. The mean age at clozapine initiation was 34 years. The majority were African-American (73% [n = 19]), with more men than women (73% [n = 19] vs 27% [n = 7]). The mean lowest ANC value was not significantly different after clozapine initiation compared to before (1.5×10^3 cells/mm^3 and 1.4×10^3 cells/mm^3, respectively; $P = .22$). The overall mean ANC was significantly higher after initiation than before (2.63×10^3 cells/mm^3 and 2.13×10^3 cells/mm^3, respectively; $P < .001$). There were no cases of severe neutropenia (ANC $< 0.5 \times 10^3$ cells/mm^3), and no patient was discontinued for falling below modified guideline limits. There were fewer occurrences of mild neutropenia (ANC $< 2.0 \times 10^3$ cells/mm^3) after clozapine initiation than before (16.0% and 31.4%, respectively; $P < .001$). There were also fewer occurrences of moderate neutropenia (ANC $< 1.5 \times 10^3$ cells/mm^3), with 2.1% after clozapine and 13.3% before ($P < .001$).
CONCLUSIONS: Twenty-six patients with benign neutropenia were safely treated with clozapine. Pre-clozapine neutropenia did not predict increased risk for severe neutropenia with clozapine. Patients had significantly fewer episodes of mild and moderate neutropenia after receiving clozapine compared to before.

Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia: A Meta-Analysis of Randomized Controlled Trials
Wei Zheng, Yu-Tao Xiang, Xin-Hu Yang, Ying-Qiang Xiang, Jose de Leon
Journal of Clinical Psychiatry 2017 March 28
OBJECTIVE: To meta-analyze randomized controlled trials (RCTs) for the efficacy and safety of adjunctive antiepileptic drugs (AEDs) to augment clozapine therapy for treatment-resistant schizophrenia.
DATA SOURCES: The search included databases in English (PubMed, PsycINFO, Embase, and Cochrane Library databases and the Cochrane Controlled Trials Register) and in Chinese (China Journal Net [CJN], WanFang, and China Biology Medicine [CBM]) and references from retrieved articles. The databases were searched using dates inclusive from their onset until January 1, 2016, for terms reflecting (a) schizophrenia, (b) clozapine, and (c) adjunctive drugs.

STUDY SELECTION: From 1,969 potentially relevant articles, 21 articles describing 22 RCTs were selected.
DATA EXTRACTION: Two independent investigators extracted data for a random-effects meta-analysis and assessed the quality of the studies using risk of bias and the Jadad scale. Standard mean difference, risk ratio (RR) ± 95% confidence intervals (CIs), and the number needed to harm (NNH) were used.
RESULTS: A total of 22 RCTs (N = 1,227) with 4 AEDs (topiramate [5 RCTs, n = 270], lamotrigine [8 RCTs, n = 299], sodium valproate [6 RCTs, n = 430], and magnesium valproate [3 RCTs, n = 228]) were analyzed. The means weighted by sample size were 12.1 weeks for treatment duration, 36.2 years for age, and 61% for male frequency. Significant superiority in total psychopathology was observed for topiramate (P < .0001), lamotrigine (P = .05), and sodium valproate (P = .002), compared to clozapine monotherapy. After removing outliers, the positive effect of sodium valproate remained, but the positive effect of lamotrigine disappeared (P = .40). Significantly improved efficacy in positive and general symptom severity was observed for topiramate (P = .04 and P = .02, respectively) and sodium valproate (P = .009 and P = .003, respectively). There were no significant differences regarding adverse drug reactions and all-cause discontinuations except for topiramate, which was associated with more all-cause discontinuations (RR = 1.99; 95% CI, 1.16 to 3.39; P = .01; I^2 = 0%; NNH = 7).
CONCLUSIONS: Sodium valproate augmentation was efficacious and safe. Topiramate augmentation had a too-high discontinuation rate. High-quality RCTs are needed to inform clinical recommendations.