With the Demise of REMS, Psychiatrists Must Start Prescribing More Clozapine

Steve Olson, MD
Adjunct Professor
Psychiatry and Behavioral Sciences

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I have no financial disclosures

I will be discussing off-label use of clozapine and medication associated with its use

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Advantages of clozapine

- More effective in reducing symptoms in treatment-resistant psychosis
- Higher patient satisfaction and adherence
- Reduces suicidal and/or aggressive behavior
- Decreased all-cause mortality
- Low risk for motor side effects
- Antidepressant and mood-stabilizing effects
- Reduction in substance misuse

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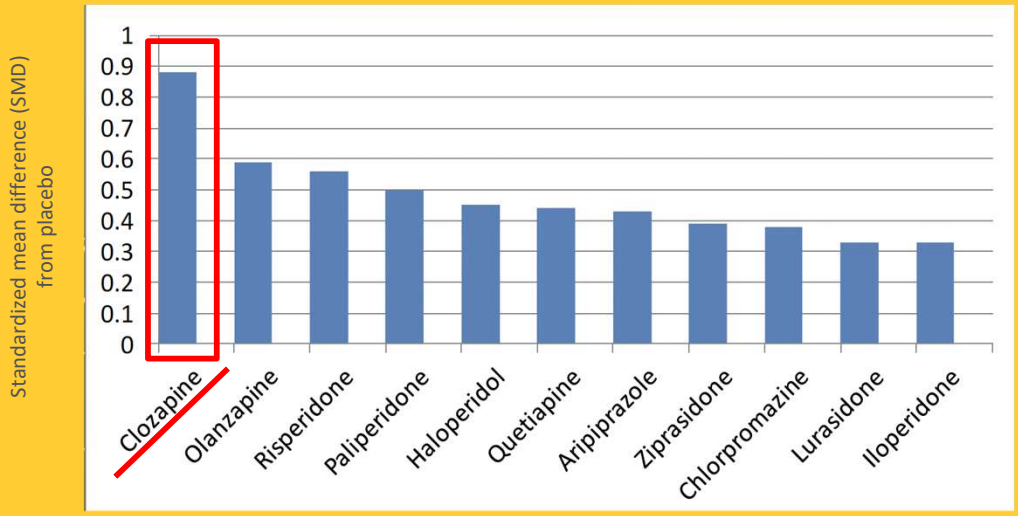
What makes clozapine different?

Clozapine is our most effective medication for psychosis



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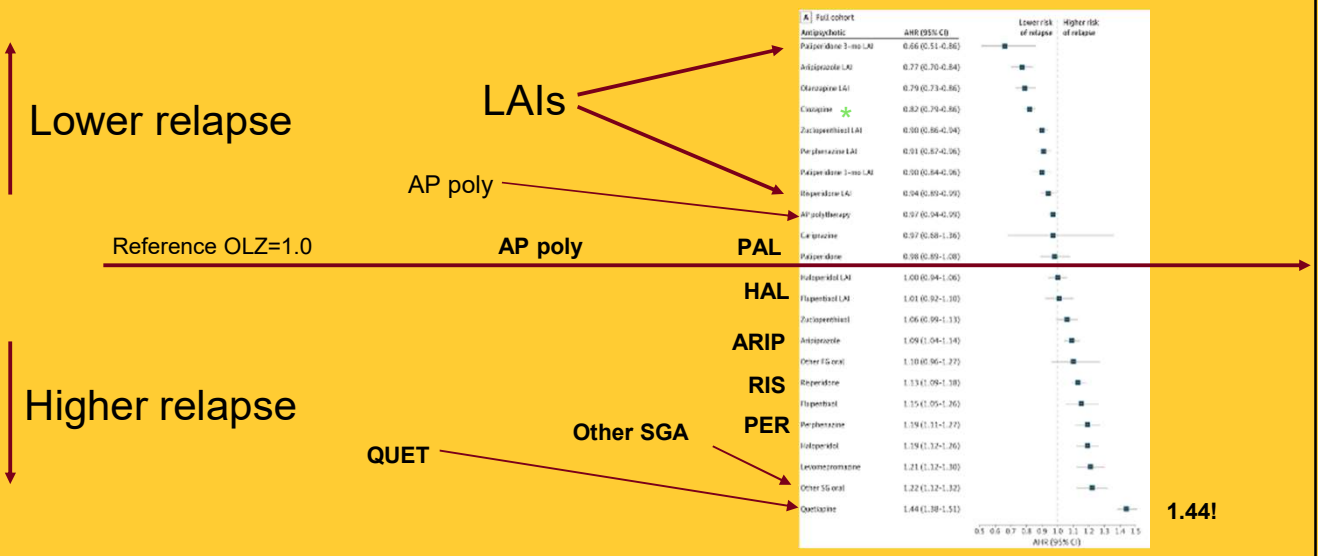
Relapse Rates for various AP



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Patients' Attitudes to Clozapine

- Patients consistently rate CLZ highly
  - 86% feel better
  - 89% prefer CLZ
  - 87% think advantages outweigh disadvantages
- Physicians underrate patients' acceptance
  - Believe blood draws are more onerous than pts. Do
  - Think sedation is more of a problem than pts.

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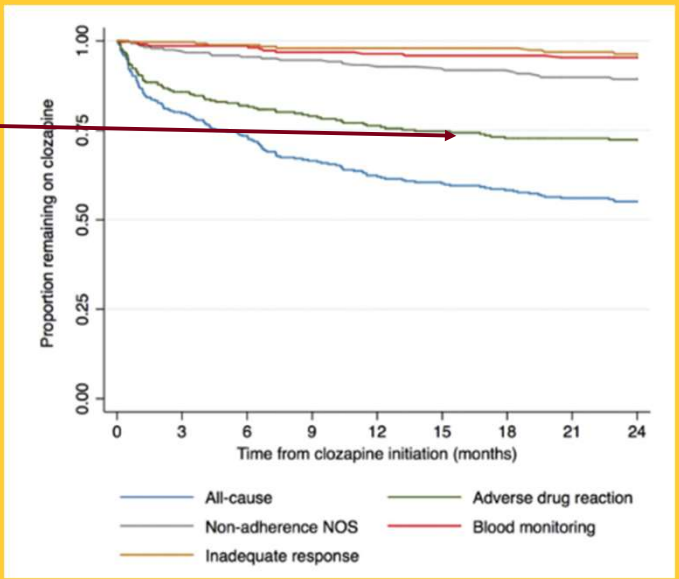
Why do Patients Stop Clozapine?

- Very few stop due to lack of response or blood monitoring
- Majority due to adverse events
- Mean time to D/C=6 months; 20% < 3 months
- Reasons for D/C were categorized into clinician- vs. patient-led decision
- Frequent discontinuation by MD for side effects which could be managed better and/or do not mandate D/C
- Socially deprived neighborhoods led to more patient-led D/C rates

Legge et al., 2016 SCZResearch



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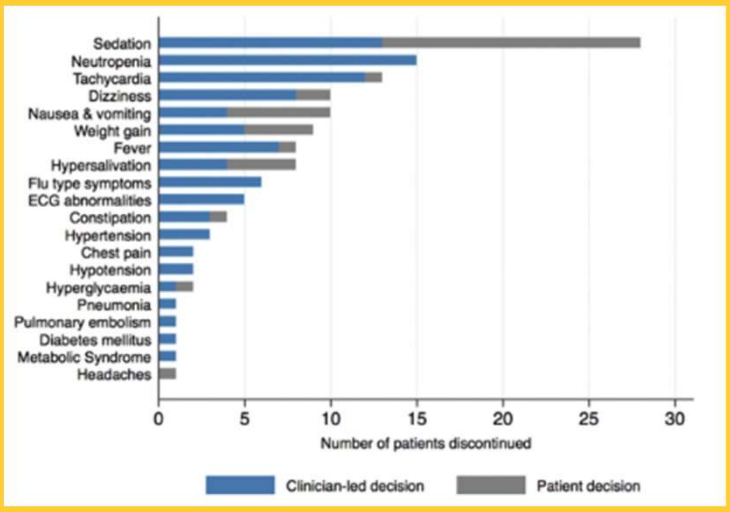
Why do Patients Stop Clozapine?

- Sedation accounted for 20% of discontinuation due to adverse events (AE), 50/50 patient vs. MD-led
- Patient-led D/C: nausea, hypersalivation, wt. gain
  - Early and aggressive Tx
- MD-led D/C: low ANC, tachycardia, flu-like Sx, dizzyness
  - Better education of MDs

Legge et al., 2016 SCZResearch



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When should we use clozapine?

- Treatment-resistant schizophrenia
  - When **two or more** other antipsychotic medications have been tried and were not effective
  - Approximately 30% of patients with schizophrenia
- Suicidal thoughts or aggressive behavior not responsive to treatment
- Other forms of psychosis: schizoaffective, unspecified psychosis, unipolar (MDD) and bipolar mood disorders
- Psychoses with movement disorders (tardive dyskinesia, catatonia, Parkinson's)

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Why isn't clozapine prescribed more often in the US?

Hesitance by providers / system

- Lack of familiarity/training with clozapine
- Concerns about side effects
- Many patients respond "enough" to other medications
- ~~Paperwork burden of working with REMS~~
- Lack of financial incentive in our current healthcare system

Hesitance by patients/families

- Concerns about side effects
- Fear or dislike of blood draws
- Lack of awareness of the benefits
- Lack of awareness of impact of illness "anosognosia"
- Logistics of getting to lab

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EASE into clozapine

- Early introduction of clozapine in the illness
- Assertive monitoring and interventions for side effects
- Slow titration and optimum dosing informed by therapeutic drug concentrations
- Engagement and support of patients and their caregivers.

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Clozapine Initiation

- Baseline Labs: CBC w/diff, EKG, CRP-Inflam, troponin
- Slow titration to minimize adverse effects (sedation, hypotension)
  - 25 mg/week if possible, monitor CRP and troponin with fast titration to identify early
- Most/all of the daily dose at bedtime
- Target dose lower (~150-200 mg/d), maintain current AP up to 100 mg daily, then slowly taper
- Address side effects promptly to maximize tolerability

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Major Adverse Effects

- GI hypomotility (constipation)
- Myocarditis
- Metabolic effects
- Severe neutropenia
- Seizures
- Sedation
- Hypersalivation

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Clozapine-induced GI Hypomotility (GIH)

- Avoid anticholinergics
  - Benztropine (Cogentin®), Trihexphenidyl (Artane®)
- Use topical AC preparations for drooling instead
  - Atropine
  - Ipratropium spray
- No fiber supplements like Metamucil

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Porirura Protocol for GI hypomotility

- Start regular docusate 100 mg QD +Senna (Senakot)
- Monitor bowel function regularly (actual BM, not subjective reporting
- Increase Sennakot by 1 tab Q 2 days to max 4
- If still constipated, rectal exam for impaction
- Add polyethylene glycol (Miralax) 18 g BID
- Enemas if no BM in 2 days
- Consider a guanylate cyclase 2C agonist, e.g. Linzess®, Trulance®

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Sedation

- All or most of daily dose at bedtime
- Slow titration
- If too groggy on waking OR late PM breakthrough Sx, add or inc. daytime dose
- Judicious caffeine
- Rarely add (ar)modafinil

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Metabolic Effects

- Patient diet and lifestyle education
- Start metformin 500-1000 BID
- Exercise and activity regimen
- Next level: GLP1 agonists, etc.

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Hypersalivation

- Patient education about managing drooling at night
- Avoid systemic anticholinergics, e.g. benztropine
- Topical atropine drops or ipratropium spray
- Elevate head of bed
- Botox injections in parotid and salivary glands effective for severe cases

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Other Benefits of Using Clozapine

- Greater patient and caregiver satisfaction
- Rewarding cases to manage through what can be a life-changing experience
- Practice at the top of your license
- Make use of your medical school education
- Cost-effective, can free up more funding for other conditions
- Prevent treatment resistance

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