

FIRST OF 3 PARTS

# Rediscovering clozapine:



C. PANNELL



# After a turbulent history, current guidance on initiating and monitoring

## FDA's overhaul of management guidelines is good reason to get reacquainted

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### Disclosures

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**A**lthough clozapine is the medication with the clearest benefits in treatment-resistant schizophrenia, many eligible patients never receive it. In the United States, 20% to 30% of patients with schizophrenia can be classified as treatment resistant, but clozapine accounts for <5% of antipsychotics prescribed.<sup>1,2</sup> Clinicians worldwide tend to under-prescribe clozapine<sup>3</sup>—a reluctance one author coined as “clozaphobia.”<sup>4</sup>

Admittedly, clozapine has had a turbulent history—both lauded as a near-miracle drug and condemned as a deadly agent. The FDA has overhauled its prescribing and monitoring guidelines, however, offering psychiatrists a perfect opportunity to reacquaint themselves with this potentially life-changing intervention.

We begin this article with clozapine's story, then spotlight new terrain the FDA created in 2015 when the agency introduced the Clozapine Risk Evaluation and Mitigation Strategy (REMS). Our goal in the 3 articles of this series is to deepen your appreciation for this tricyclic antipsychotic and provide practical clinical guidance for using it safely and effectively.

### Setbacks, but the drug has an enduring presence

The 1950s was an exciting era of exploration for new psychotropic medications. While searching for tricyclic antidepressants, Wander Laboratories discovered neuroleptic tricyclics, with clozapine identified in 1959 (*Figure 1, page 44*). Haloperidol's development and release in the 1960s reinforced the prevailing dogma of the time that effective neuroleptics correlated with extrapyramidal symptoms, thus limiting interest in the newly discovered, but pharmacologically unique, clozapine.

continued



## Clozapine

### Clinical Point

REMS created a centralized registry of all U.S. patients treated with clozapine and made changes to prescribing and monitoring guidelines



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Figure 1

## The 60-year-plus timeline of clozapine

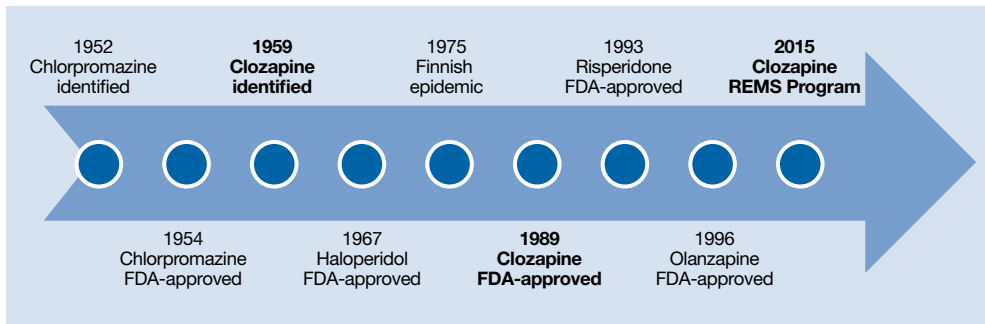


Table 1

### 3 Steps to prescriber certification in the Clozapine REMS Program

Step 1	Complete and submit the 1-time <i>Clozapine REMS Prescriber Enrollment Form</i>
Step 2	Review <i>Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers</i>
Step 3	Pass the <i>Knowledge Assessment for Healthcare Providers</i>
<b>Source:</b> Clozapine REMS, available at <a href="http://www.clozapinerems.com">www.clozapinerems.com</a>	

Throughout the 1960s, most research on clozapine was published in German, with less of an international presence.<sup>5</sup>

**Agranulocytosis deaths.** Clozapine earned its scarlet letter in 1975, when 8 patients in Finland died of agranulocytosis.<sup>6</sup> Sandoz, its manufacturer, withdrew clozapine from the market and halted all clinical trials. The Finnish epidemic triggered detailed investigations into blood dyscrasias and early identification of agranulocytosis associated with clozapine and other antipsychotics.<sup>7</sup>

Clozapine endured only because of its unique efficacy. When psychiatrists witnessed relapses in patients who had to discontinue clozapine, some countries allowed its use with strict monitoring.<sup>5</sup> The FDA kept clozapine minimally available in the United States by allowing so-called “compassionate need programs” to continue.<sup>7</sup>

**New data, FDA approval.** Two studies in 1987 and 1988 that compared clozapine

with chlorpromazine for treatment-refractory schizophrenia demonstrated clozapine’s superior effect on both negative and positive symptoms.<sup>8,9</sup> The FDA approved clozapine for refractory schizophrenia in 1989, and clozapine became clinically available in 1990.

Initially, the high annual cost of clozapine’s required “bundle” (\$8,900 per patient for medication and monitoring) led to political outcry. As patients and their family struggled to afford the newly released medication, multiple states filed antitrust lawsuits. A federal court found both the manufacturer and individual states at fault and required expanded access to clozapine and its necessary monitoring. National clozapine registries were formed, and bundling was eliminated.<sup>7</sup>

### The clozapine REMS program

Six clozapine registries operated independently, each managed by a different manufacturer,<sup>10</sup> until the FDA introduced REMS in September 2015. The REMS program created a centralized registry to monitor all U.S. patients treated with clozapine and made important changes to prescribing and monitoring guidelines.<sup>11,12</sup> It also incorporated the National Non-Rechallenge Master File (NNRMF).

Initially, the REMS program was scheduled for rollout October 12, 2015, the closing date of the 6 registries. Since November 2015, pharmacies have been required to register with the program to dispense clozapine. A similar registration deadline

for clozapine prescribers was extended indefinitely, however, because of technical problems. Once the deadline is finalized, all clozapine prescribers must complete 3 steps to be certified in the REMS program (*Table 1*).<sup>11</sup>

**New requirements.** Certified clozapine prescribers will have new responsibilities: enrolling patients and submitting lab results. They can designate someone else to perform these tasks on their behalf, but designees must enroll in the REMS program and the prescriber must confirm the designee. Pharmacists can no longer enroll patients for clozapine therapy unless they are confirmed as a prescriber designee. For outpatients, the absolute neutrophil count (ANC) must be reported before the pharmacy can dispense clozapine. For inpatients, the ANC must be reported within 7 days of the patient's most recent blood draw.

Once the system is fully operational, Social Security numbers will no longer be used as patient identification for dispensing clozapine. Instead, outpatient pharmacies will obtain a predispose authorization, or PDA, from the REMS program. A person initiated on clozapine as an inpatient must be re-enrolled after discharge by their outpatient prescriber.

The REMS program includes information about clozapine patients who were maintained through the 6 registries, and these patients have been allowed to continue clozapine treatment. Data pertaining to patients last prescribed clozapine before October 1, 2012, did not transfer into the new system unless their name was on the NNRMF.

**CASE**

**Is Mr. A a candidate for clozapine?**

Age 28, with schizophrenia, Mr. A is highly disorganized and psychotic when brought to the emergency room by police for inappropriate behavior. His family arrives and reports that similar events have occurred several times over the past few years. Mr. A's outpatient psychiatrist has prescribed 3 different antipsychotic medications at adequate dosages, including 1 long-acting injectable, but Mr. A has remained consistently symptomatic.

**Table 2**

**Recommended baseline screening before you initiate clozapine therapy**

Body weight
Complete blood count with differential, including absolute neutrophil count
Comprehensive metabolic panel, including renal function, hepatic function, protein levels, and electrolytes
ECG <sup>a</sup>
Fasting glucose
Fasting lipids
Orthostatic blood pressure
<sup>a</sup> Strongly consider, with patient safety in mind

Although disorganized and psychotic, Mr. A does not meet criteria for long-term involuntary hospitalization. His family wants to take him home, and the treatment team discusses clozapine as an anti-psychotic option. Mr. A and his family agree to a trial of clozapine during voluntary hospitalization, but they would like him home within a week to attend his sister's birthday party.

The treatment team decides to initiate clozapine and monitor his response in a controlled setting for a few days before transitioning him to outpatient care.

**Initiating clozapine therapy**

The case of Mr. A exemplifies a situation in which initiating clozapine is a reasonable clinical consideration. As the first step, we recommend checking baseline lab values and vital signs (*Table 2*), keeping in mind that the REMS program requires a baseline ANC within 7 days of initiating clozapine. When working with a highly disorganized or agitated patient, balance benefits of testing against the risk of harm to staff and patient.

REMS guidelines recommend a baseline ANC  $\geq 1,500/\mu\text{L}$  for a new patient starting clozapine, except when benign ethnic neutropenia (BEN) has been confirmed. (Initiation guidelines for BEN are discussed later in this article.)

**Clinical Point**

**REMS requirements give clozapine prescribers responsibility for enrolling patients and submitting lab test results**

continued



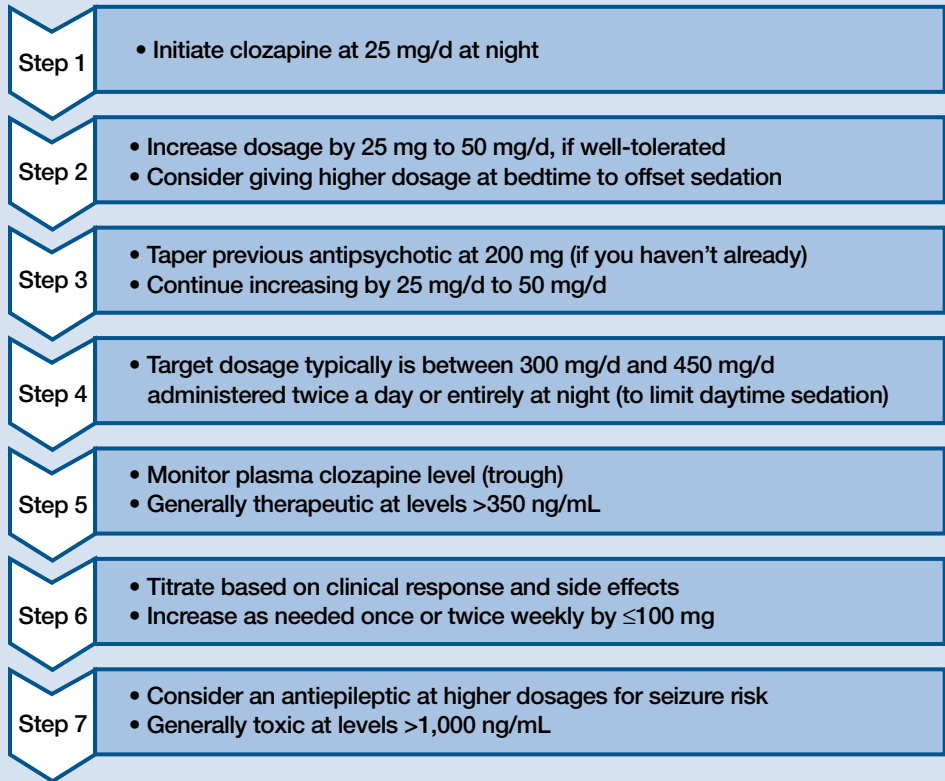
## Clozapine

### Clinical Point

The 3 oral forms of clozapine are tablet, disintegrating tablet, and suspension; all forms can be titrated using the schedule for tablets

Figure 2

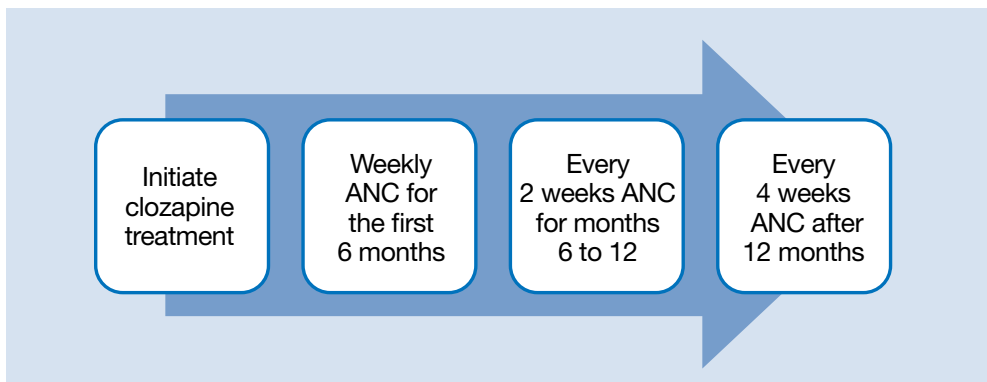
## Follow these 7 recommended steps for initiating clozapine



Source: Adapted from reference 14

Figure 3

## Monitoring guidelines for patients taking clozapine



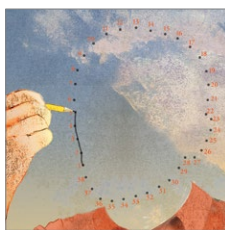
ANC: absolute neutrophil count

Source: Adapted from reference 14

**Dosing alternatives.** We recommend following the manufacturer's dosing guidelines when initiating clozapine (Figure 2).<sup>13,14</sup> Three oral forms are available: tablet, disintegrating tablet, and suspension. All can be titrated using the schedule suggested with tablets.

The disintegrating tablets or suspension might be beneficial for a patient with either:

- a history of "cheeking" or otherwise disposing of tablets
- a medical condition that affects swallowing or absorption.



## Clozapine

### Clinical Point

Consider interrupting clozapine therapy if the absolute neutrophil count falls below 1,000/ $\mu$ L and clozapine is the suspected cause

### Related Resources

- Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program <https://www.clozapinerems.com/CpmgClozapineUI/home.u>.
- Clozapine REMS Program. What's new with clozapine: an overview. [https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/WhatsNEWwithClozapine\\_An%20Overview.pdf](https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/WhatsNEWwithClozapine_An%20Overview.pdf).
- Clozapine REMS Program. Clozapine and the risk of neutropenia: a guide for healthcare providers. [https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine\\_REMS\\_HCP\\_Guide.pdf](https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_HCP_Guide.pdf).

### Drug Brand Names

Chlorpromazine • Thorazine	Clozapine, tablets
Clozapine, orally disintegrating tablets • FazaClo	• Clozaril
Clozapine, oral suspension	Haloperidol • Haldol
• Versacloz	Olanzapine • Zyprexa
	Risperidone • Risperdal

The disintegrating tablet is available in 12.5-mg, 25-mg, 100-mg, 150-mg, and 200-mg doses. It dissolves without requiring additional liquids. Each mL of the suspension contains 50 mg of clozapine.

**Rapid titration?** One group, working in Romania, examined the safety and efficacy of rapid titration of clozapine in 111 inpatients with schizophrenia.<sup>15</sup> In the absence of additional studies, we do not recommend routine rapid titration of clozapine.

### Monitoring: Greater flexibility

Under the REMS program, laboratory monitoring of clozapine treatment must continue indefinitely. If not, pharmacies cannot dispense clozapine. Fortunately, the ANC is the only lab value tracked by the registry, and the frequency of required blood draws decreases over time (*Figure 3, page 46*).

Other guideline changes provide clinicians with greater flexibility to make patient-specific treatment decisions; for example, the allowable ANC to con-

tinue clozapine therapy has decreased. Usually, clozapine therapy should be interrupted for an ANC <1,000/ $\mu$ L if the prescriber suspects clozapine-induced neutropenia. Even when the ANC drops below 1,000/ $\mu$ L, however, prescribers can now continue clozapine treatment if they consider the benefits to outweigh risks for a given patient.

Separate guidelines now exist for patients with BEN, most commonly observed in persons of certain ethnic groups. BEN typically is diagnosed based on repeated ANC values <1,500/ $\mu$ L over several months. Patients with BEN do *not* have an increased risk of oral or systemic infections, as occur with other congenital neutropenias.<sup>16</sup> In patients with BEN, clozapine therapy:

- can be initiated only after at least 2 baseline ANC measurements  $\geq$ 1,000/ $\mu$ L
- should be interrupted for an ANC <500/ $\mu$ L if the prescriber suspects clozapine-induced neutropenia.

Substantial drops in ANC no longer require action (repeat lab draws) unless the drop causes neutropenia. Prescribers will receive an automated notification any time a patient experiences neutropenia that is considered mild (ANC 1,000 to 1,499/ $\mu$ L), moderate (ANC 500 to 999/ $\mu$ L), or severe (ANC <500/ $\mu$ L).

The NNRMF list is no longer definitive. All patients are now eligible for rechallenge, assuming they meet the new clozapine initiation criteria.

### Next, when rediscovering clozapine: Adverse effects

Despite an intimidating list of side effects and interactions, clozapine is associated with a significant reduction in patients' risk of overall mortality. In Part 2 of this series in the August 2016 issue, we discuss early

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## Bottom Line

Clozapine remains the most efficacious, but most tedious, antipsychotic available to psychiatrists. New prescribing and monitoring guidelines provide less cumbersome requirements and allow clinicians increased flexibility in decision-making.



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identification of clozapine's adverse effects and provide guidance for management.

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