1 The Efficacy Story: Treatment-Resistant Schizophrenia, Psychogenic Polydipsia, Treatment-Intolerant Schizophrenia, Suicidality, Violence, Mania and Parkinson's Disease Psychosis

QUICK CHECK

INTRODUCTION

The 60th anniversary of clozapine's synthesis by Schmutz and Eichenberger at Wander Pharmaceuticals was celebrated in 2018, although the chemists involved hoped that their tricyclic compound HF-1854 would possess antidepressant effects [1]. In January 1961, the first pharmacological report on HF-1854 described an agent with sedative and antiadrenergic properties that resembled chlorpromazine, but which did not induce catalepsy [1]. Further animal testing reported in December 1961 established a range of activities comparable to chlorpromazine but without the catalepsy induction seen with haloperidol. In 1962 the first open clinical trial of HF-1854 found limited efficacy at the dose of 160 mg TID ($n = 19$), but later that year Gross and Langer in Vienna found good results in 21 of 28 patients at similar dosing, again without neurological adverse effects [2]. Further trial reports to Wander

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PRINCIPLES

- Clozapine is the only effective antipsychotic for treatment-resistant schizophrenia. When treatment resistance is rigorously defined using all three Kane criteria, the response rate to most antipsychotics is < 5%, and for olanzapine 7%.
- Delaying clozapine initiation beyond 3 years after treatment resistance is identified reduces the likelihood of response.
- Compared to other antipsychotics, real-world data indicate that clozapine-treated patients have lower rehospitalization rates, and decreased mortality from all causes (natural and unnatural).
- Clozapine is uniquely effective in schizophrenia patients with psychogenic polydipsia.
- Clozapine is effective for schizophrenia patients with suicidality on the basis of a large clinical trial vs. olanzapine. Clozapine has an approved indication for this purpose in the US.
- Clozapine's impact on suicidality and aggression is independent of the antipsychotic effect.
- Clozapine has proven efficacy in treatment-resistant mania when used adjunctively with mood-stabilizing medications, and is effective in nonpsychotic bipolar patients.
- Prior to the development of pimavanserin, clozapine was the antipsychotic with the strongest evidence for efficacy and tolerability in Parkinson's disease psychosis.

Pharmaceuticals in 1966 by Hippius in Berlin and Engelmeier in Vienna indicated that this was an effective but sedating antipsychotic that appeared free of neurological side effects. Wander completed further toxicological assays in 1967 and embarked on multiple clinical trials resulting in product registration in 1971, and marketing the following year under the trade name Leponex [1]. A spate of severe neutropenia cases from Finland in 1975 led to clozapine's withdrawal from the market in most countries, although it was available under humanitarian programs with hematological monitoring [3].

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Three double-blind studies comparing clozapine to other antipsychotics were published in the 1970s and 1980s based on perceived benefit in those who did not respond to other agents, or improved tolerability in patients with a history of severe intolerance to D_2 antagonism (i.e. akathisia, parkinsonism, tardive dyskinesia (TD) or neuroleptic malignant syndrome (NMS)). While clozapine was clearly better tolerated and more effective than chlorpromazine among those with a history of D_2 sensitivity [4], the two large efficacy trials used modest dosages of the comparator antipsychotics (chlorpromazine 360 mg/day, haloperidol 7.6 mg/day), raising doubts about clozapine's greater effectiveness [5]. The latter question was definitively settled with publication of the pivotal clozapine trial for treatment-resistant schizophrenia in 1988, using criteria elaborated by Dr. John Kane for this purpose [6]. A crucial element of the trial design was the third criterion for treatment resistance: demonstrating in a prospective manner failure to respond to high levels of D_2 antagonism. Fewer than 2% of patients met response criteria in the prospective haloperidol arm of the Kane study (mean dose 61 mg/day), while 80% were nonresponders and 18% intolerant of high-dose haloperidol. Using only those schizophrenia patients who met all three of the treatment-resistance criteria ($n = 268$), response rates in the short (6-week) double-blind, randomized trial were 4% for the chlorpromazine arm vs. 30% for the clozapine group [6]. Additional experience over the next decade combined with insights regarding therapeutic plasma levels has increased the expected clozapine response rate to at least 40% in longer-term studies, with values up to 60% reported [7]. Clozapine has also demonstrated efficacy in schizophrenia patients with psychogenic polydipsia, an effect seen with doses as low as 300 mg/day [8].

Box 1.1 Essential Components of the Kane Definition of Treatment-Resistant Schizophrenia for Patients Enrolled in the Pivotal Clozapine Trial

1. At least three periods of treatment in the preceding 5 years with antipsychotics (from at least two different chemical classes) at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief.
2. No period of good functioning within the preceding 5 years.
3. Failure to respond to a prospective high-dose trial of a typical antipsychotic (haloperidol at doses up to 60 mg/day or higher administered with benztropine 6 mg/day). Response was defined as a 20% decrease in the Brief Psychiatric Rating Scale (BPRS) total score plus either a post-treatment Clinical Global Impression (CGI) severity rating of mildly ill (≤ 3) or a post-treatment BPRS score ≤ 35.

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The unique benefits of clozapine extend beyond treatment-resistant schizophrenia and include a number of other uses, many of which are supported by rigorous double-blind, placebo or active comparator trials. In some instances, the value of clozapine lies in its low affinity for D_2 receptors, thus permitting treatment of schizophrenia patients intolerant of D_2 antagonism, or Parkinson's disease psychosis (PDP) patients. For other applications, the underlying mechanism for clozapine's effectiveness is unknown, but it appears independent of the antipsychotic effect when employed for treatment-resistant mania, in schizophrenia patients with persistent aggression, and in schizophrenia patients with a history of suicidality. By mastering the details of hematologic monitoring and management of adverse effects, clinicians have a range of evidence-based uses for clozapine in difficult-to-treat patient groups.

A Treatment-Resistant Schizophrenia

While inconvenient, criterion 3 of the Kane 1988 criteria is central to a research definition of treatment resistance. Studies using "modified Kane criteria" that lack this crucial element report unrealistically high response rates for atypical antipsychotics other than clozapine. The enormous impact of criterion 3 can be seen in the three double-blind studies of olanzapine for treatment-resistant schizophrenia (Table 1.1). Response rates to olanzapine at doses up to 50 mg/day were 0% and 7% in the two studies that included criterion 3 [9,10], but response to olanzapine was 50% when this step was omitted [11].

Unfortunately the literature is littered with numerous papers in which patients with varying degrees of treatment resistance and intolerance are grouped together, leading the unwary reader to question clozapine's benefit in treatment-resistant patients. Adding to the confusion was a 2016 meta-analysis that included literally any definition of treatment resistance in its examination of the literature, and reviewed studies that also enrolled treatment-intolerant patients [12]. Although that meta-analysis did not change perceptions regarding clozapine's efficacy for treatment-resistant schizophrenia, it reinforced the concept that one must take a jaundiced view of studies for treatment-resistant schizophrenia that do not subject patients to a prospective antipsychotic trial and rely solely on historical records of prior antipsychotic treatment. Aside from treatment resistance, there are many reasons that patients may fail to respond adequately to an antipsychotic, with nonadherence, underdosing and kinetic issues playing significant roles. To further emphasize this point, in a recent outpatient

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Table 1.1 Double-blind olanzapine trials using strict criteria for treatment-resistant schizophrenia.

Reference	Population included	% Responders
Conley et al., 1998 [9]	Treatment-resistant schizophrenia, defined by Kane criteria: • Inpatients with poor function for ≥ 5 years • Historical failure with two typical antipsychotics for at least 6 weeks on daily doses > 1000 mg/day chlorpromazine equivalents • **Failure of a prospective 6-week haloperidol trial at daily doses of 10–40 mg** **Study method:** 8-week fixed-dose trial of olanzapine 25 mg/day vs. chlorpromazine 1200 mg/day (*n* = 84). Response defined as ≥ 20% improvement in the total BPRS score, endpoint BPRS score ≤ 35, and a CGI severity score ≤ 3.	Olanzapine 7%[1] Chlorpromazine 0%
Conley et al., 2003 [10]	Treatment-resistant schizophrenia, defined by Kane criteria: • Inpatients with poor function for ≥ 5 years • Historical failure with two typical antipsychotics for at least 6 weeks on daily doses > 1000 mg/d chlorpromazine equivalents • **Failure of a prospective 6-week haloperidol trial at daily doses of 10–40 mg** **Study method:** Double-blind, randomized crossover study of olanzapine 50 mg/day vs. clozapine 450 mg/day (with option for reduction to 30 mg/day olanzapine or 300 mg/day clozapine for tolerability) (*n* = 23). Patients received 8 weeks on olanzapine or clozapine including a 2-week titration to the target dose. At the end of 8 weeks subjects were switched to the other medication. Response was defined as ≥ 20% improvement in total BPRS score, and a final BPRS score ≤ 35 or a 1 point improvement on the CGI severity score.	Olanzapine 0% Clozapine 20%
Meltzer et al., 2008 [11]	Treatment-resistant schizophrenia, defined as historical failure of two or more trials of typical or atypical antipsychotics "with usually adequate doses" for at least 6 weeks. **Study method:** 1-year double-blind study of olanzapine up to 45 mg/day and clozapine up to 900 mg/day (*n* = 40). Response was defined as ≥ 20% improvement in total PANSS score at 6 months, or at 6 weeks if drop out was due to reasons other than lack of efficacy.	Olanzapine 50%[2] Clozapine 60%

Comments

1. Twenty-seven olanzapine-treated subjects who failed to respond in this study were titrated on open-label clozapine and followed for 8 weeks. Using the same response definition as the prior trial, 41% met response criteria on clozapine [71].
2. No prospective trial of high-dose typical antipsychotic (Kane criterion 3).

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study of 99 schizophrenia patients deemed treatment-resistant, 35% had plasma antipsychotic levels that were subtherapeutic [13].

One positive outcome of the confusing 2016 meta-analysis was a sharpening of the debate regarding the need to define treatment resistance in research and clinical settings [14]. There is little question that, when rigorously defined using all three Kane criteria, the anticipated response rate to antipsychotics other than clozapine is < 5%, compared to rates ≥ 40% for clozapine. Because implementing criterion 3 is often impractical for routine clinical care, a consensus panel published guidelines in 2017 to help clinicians ascertain when patients are treatment-resistant. Included in this recommendation is that the term "refractory" no longer be used (Table 1.2).

Table 1.2 Consensus criteria for defining an adequate antipsychotic trial in resistant schizophrenia patients [14].

	Minimum requirement	Optimum requirement
Duration	• ≥ 6 weeks at a therapeutic dosage • Record minimum and mean (SD) duration for each treatment episode	• ≥ 6 weeks at a therapeutic dosage • Record minimum and mean (SD) duration for each treatment episode
Dosage	• Equivalent to ≥ 600 mg of chlorpromazine per day • Record minimum and mean (SD) dosage for each drug	• Equivalent to ≥ 600 mg of chlorpromazine per day • Record minimum and mean (SD) dosage for each drug
Number of antipsychotics	• ≥ Two past adequate treatment episodes with different antipsychotic drugs • Specify median number of failed antipsychotic trials	• ≥ Two past adequate treatment episodes with different antipsychotic drugs, and at least one utilizing a long-acting injectable antipsychotic (for at least 4 months) • Specify median number of failed antipsychotic trials
Current adherence	• ≥ 80% of prescribed doses taken • Adherence should be assessed using at least two sources (pill counts, dispensing chart reviews, and patient/caregiver report) • Antipsychotic plasma levels monitored on at least one occasion • Specify methods used to establish adherence	• Same as the minimum criteria, with the addition of trough antipsychotic serum levels measured on at least two occasions separated by at least 2 weeks (without prior notification of patient)

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These criteria emphasize that clinicians must be mindful of high nonadherence rates in schizophrenia patients before concluding that prior antipsychotic trials were failures. When prior trials lacked plasma levels, or had features associated with antipsychotic nonadherence (e.g. missed refills, homelessness, substance use, no documented adverse effects), it is not unreasonable to conduct a trial with a long-acting injectable and plasma level monitoring to confirm adequate antipsychotic exposure. If prior trials employed relatively weaker D_2 antagonists (e.g. quetiapine) or a D_2 partial agonist (e.g. aripiprazole, brexpiprazole, cariprazine), and there is no history of unusual D_2 sensitivity at routine doses, one should consider use of a stronger D_2 antagonist for the depot formulation. Clinicians can be guided by the literature in cases where exploring higher antipsychotic plasma levels appears feasible in a nonresponding and adherent patient (by plasma levels) who is not exhibiting dose-limiting adverse effects [15]. Nonetheless, despite a clinician's best efforts, at least 20–30% of schizophrenia patients will be inadequate responders to nonclozapine antipsychotics.

Outside of the academic sphere, there are large data sets that substantiate clozapine's effectiveness in 'real-world' circumstances. Table 1.3 summarizes the latest and best-designed of these studies. Two of these studies examined enormous samples of schizophrenia patients (18,869 and 29,823) for up to 8 years [16,17], while another looked at two matched cohorts of 3123 schizophrenia patients who met clinically defined criteria for treatment resistance [18].

By selecting those patients who would be deemed treatment-resistant by routine clinical standards, the latter study emphasizes the benefits of clozapine compared to other antipsychotics for that population [18]. As opposed to the outcomes found in an inpatient research unit or highly supervised research clinic, these naturalistic data sets provide a compelling picture of clozapine's effectiveness in the hands of clinicians working with a challenging population with varying degrees of motivation, adherence and illness severity. Regardless of the treatment setting, clozapine remains the option with best chance of success for the treatment-resistant schizophrenia patient.

Impact of Delays in Commencing Clozapine

One important variable in maximizing the chance of clozapine response involves minimizing the time to initiation once the patient meets clinical criteria for treatment resistance. Given the reluctance of many clinicians to prescribe clozapine, it is not surprising that the literature documents unnecessary delays in commencing

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Table 1.3 Summary of large real-world effectiveness studies in schizophrenia 2016–2017.

Reference	Comments
Vanasse et al., 2016 [16]	**Sample:** Retrospective analysis of outcomes for 18,869 adult schizophrenia patients living in Quebec, Canada and starting an antipsychotic between January 1998 and December 2005. **Outcomes of interest:** Any mental health event (suicide, hospitalization or emergency visit for mental disorders), and any physical health event (death other than suicide, hospitalization or emergency visit for physical disorders). **Results:** Compared to FGAs, patients on quetiapine at the time of the event was associated with increased risk of mental health events (HR = 1.38, 95% CI 1.24–1.54, $p < 0.0001$) and also of physical health events (HR = 1.24, 95% CI 1.12–1.37, $p < 0.0001$). Patients not using any antipsychotic were also at an increased risk of mental health events (HR = 1.54, 95% CI 1.44–1.65, $p < 0.0001$), and physical health events (HR = 1.24, 95% CI 1.17–1.32, $p < 0.0001$). Clozapine was associated with slightly lower risk of mental or physical health events than FGAs, and was associated with markedly lower rates of discontinuation or antipsychotic switching compared to FGA and other SGAs.
Stroup et al., 2016 [18]	**Sample:** Retrospective examination of outcomes for 3123 adult schizophrenia patients extracted from US national Medicaid data 2001–2009 with clinical evidence of treatment resistance that required clozapine. This cohort was matched with a similar cohort of 3123 patients with clinical evidence of treatment resistance that initiated a standard antipsychotic. **Outcomes of interest:** Hospital admission for a mental disorder. Secondary efficacy outcomes included discontinuation of the antipsychotic, and use of an additional antipsychotic. **Results:** Initiation of clozapine was associated with a significantly lower rate of psychiatric hospital admission (HR = 0.78, 95% CI 0.69–0.88). Clozapine was also associated with lower rates of antipsychotic discontinuation (HR = 0.60, 95% CI 0.55–0.65), and the need for an additional antipsychotic (HR = 0.76, 95% CI 0.70–0.82).
Tiihonen et al., 2017 [17]	**Sample:** Retrospective examination of outcomes for 29,823 patients in Sweden with a schizophrenia diagnosis who were 16–64 years of age in 2006. Psychiatric outcomes were analyzed for July 1, 2006, to December 31, 2013. **Outcomes of interest:** Risk of rehospitalization and treatment failure (defined as psychiatric rehospitalization, suicide attempt, discontinuation or switch to other medication, or death). **Results:** Risk of psychiatric rehospitalization was the lowest during monotherapy with once-monthly long-acting injectable paliperidone (HR = 0.51; 95% CI 0.41–0.64), long-acting injectable zuclopenthixol (HR = 0.53, 95% CI 0.48–0.57), clozapine (HR = 0.53, 95% CI 0.48–0.58), long-acting injectable perphenazine (HR = 0.58, 95% CI 0.52–0.65), and long-acting injectable olanzapine (HR = 0.58, 95% CI 0.44–0.77) compared with no use of antipsychotic medication. Oral flupentixol (HR = 0.92, 95% CI 0.74–1.14), quetiapine (HR = 0.91; 95% CI 0.83–1.00), and oral perphenazine (HR = 0.86, 95% CI 0.77–0.97) were associated with the highest risk of rehospitalization.

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic; HR, hazard ratio.

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clozapine treatment. A clinical review of all 149 patients started on clozapine at the South London and Maudsley NHS Foundation Trust from 2006 to 2010 found that the mean delay in initiating clozapine was 47.7 months, with 36% of patients receiving antipsychotic polypharmacy and 34% receiving high-dose antipsychotic therapy during the delay [19]. A subsequent paper covering 162 clozapine starts at the Istanbul Faculty of Medicine, Department of Psychiatry noted a mean delay of 29 months after fulfilling treatment-resistance criteria [20]. While those who responded to clozapine tended to be younger, have shorter illness duration and fewer numbers of adequate antipsychotic trials before clozapine, the extent of delay in starting clozapine was an independent contributor to the odds of clozapine response [20]. The mean delay in initiating clozapine in the good response group was 21 months, compared to 47 months in those with minimal or no improvement ($p = 0.04$). Utilizing the concept that the biological onset of treatment resistance was not when the patient was finally deemed to have failed their second antipsychotic but when that period of exacerbation commenced, a group from a tertiary care inpatient hospital in Okayama, Japan analyzed data in 90 new clozapine starts who remained on treatment for at least 3 months (see Figure 1.1) [21]. Using this definition, they found that a delay in clozapine initiation of 2.8 years best predicted those who would benefit from clozapine treatment. In patients with a delay ≤ 2.8 years the response rate was 81.6%, while it fell to 30.8% in those with a delay > 2.8 years. Consistent with the Turkish data, older age and longer duration of illness were associated with lower response rates.

Clozapine and Mortality

Symptomatic exacerbation and rehospitalization are inherent to schizophrenia, but so is increased risk of mortality from all causes, natural and unnatural (i.e. accidents, suicide) [22]. Increasingly sophisticated database studies indicate that clozapine is associated with lower mortality rates than other antipsychotics, that clozapine reduces mortality from both natural and unnatural causes, and that the mortality reduction is not solely due to increased clinical monitoring or other treatment factors (Table 1.4). The impact of clozapine on mortality is only present if the patient continues on clozapine. A 2018 meta-analysis of 24 long-term mortality studies found mortality rate ratios were 44% lower in patients continuously treated with clozapine (compared to other antipsychotics), but were not significant lower in those who ever used clozapine [23]. The loss of clozapine's protective effect on mortality emerges soon after

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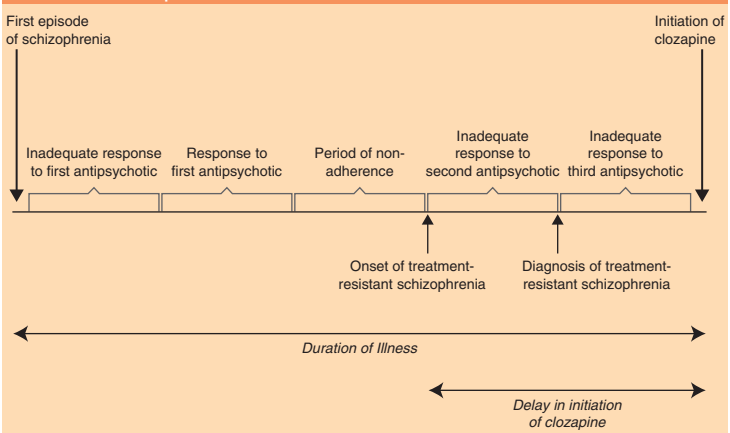
Figure 1.1. Delaying the time to starting clozapine reduces likelihood of response in resistant schizophrenia.



(Adapted from: Yoshimura, B., Yada, Y., So, R., et al. (2017). The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. *Psychiatry Research*, 250, 65–70 [21].)

treatment stoppage, with Danish data showing that mortality was highest in periods after clozapine discontinuation (HR: 2.65, 95% CI 1.47–4.78) [22].

What is interesting about this literature is that the Quebec study (Table 1.3) showed that clozapine lowered the odds of all physical health events despite subanalyses showing that current clozapine use was associated with higher risk for serious physical health events (i.e. hospitalization or death from nonpsychiatric medical causes) [16]. As noted in Chapters 7 and 9, use of clozapine is associated with constipation and sialorrhea that in some cases can result in ileus or aspiration pneumonia. As clinicians become more adept at managing those two adverse effects of clozapine, it will be interesting to note whether the mortality gap between clozapine and other antipsychotics further widens in favor of clozapine for treatment-resistant schizophrenia patients. Antipsychotic treatment is the foundation upon which patients can build skills to achieve functional goals, but such goals can only be attained if the patient remains alive. Even with clozapine's burden of somatic adverse effects, the

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Table 1.4 Summary of recent large antipsychotic mortality studies in schizophrenia.

Reference	Comments
Tiihonen et al., 2009 [32]	**Sample:** Nationwide registers in Finland were used to examine mortality in 66,881 outpatients with schizophrenia between 1996 and 2006, and to link these data with the use of antipsychotic drugs. Perphenazine was used as the comparison medication. **Outcomes of interest:** All-cause mortality using Cox regression models for the period. Secondary outcomes included mortality due to suicide and ischemic heart disease. **Results:** Compared with current use of perphenazine, the highest risk for overall mortality was recorded for quetiapine (adjusted HR = 1.41, 95% CI 1.09–1.82), and the lowest risk for clozapine (HR = 0.74, 95% CI 0.60–0.91). Use of clozapine significantly decreased risk of death by suicide (HR = 0.34, 95% CI 0.20–0.57), and did not increase risk of death due to ischemic heart disease.
Hayes et al., 2015 [72]	**Sample:** The South London and Maudsley National Health Service Foundation Trust case register linked to a national (UK) mortality database was used to identify 14,754 individuals with serious mental illnesses including schizophrenia, schizoaffective and bipolar disorders aged ≥ 15 years. **Outcomes of interest:** The effect of clozapine on mortality over a 5-year period (2007–2011) using Cox regression models for the period. **Results:** There was a significant association between being prescribed clozapine and lower mortality after controlling for numerous potential confounders including clinical monitoring associated with clozapine use and markers of disease severity (adjusted HR = 0.4, 95% CI 0.2–0.7; $p = 0.001$). For natural causes of death the adjusted HR = 0.5 (95% CI 0.2–0.9). For unnatural causes of death the adjusted HR = 0.2 (95% CI 0.05–0.9).
Wimberley et al., 2017 [22]	**Sample:** The Danish National Prescription Registry and clinical databases were used to identify a cohort of 2370 individuals with treatment-resistant schizophrenia after January 1, 1996. The cohort was followed until death, first episode of self-harm, emigration, or June 1, 2013. **Outcomes of interest:** Time to all-cause death and time to first episode of self-harm were analyzed in Cox regression models for the period. **Results:** The absence of clozapine treatment was associated with an elevated all-cause mortality (HR = 1.88, 95% CI 1.16–3.05) in adjusted models. Estimates were substantially higher for no antipsychotic treatment (HR = 2.50, 95% CI 1.50–4.17) and nonclozapine antipsychotic treatment (HR = 1.45, 95% CI 0.86–2.45*). Mortality was highest in periods after clozapine discontinuation (HR = 2.65, 95% CI 1.47–4.78). When compared with clozapine, nonclozapine antipsychotics were associated with an elevated rate of self-harm (HR = 1.36, 95% CI 1.04–1.78).
Vermeulen et al., 2019 [23]	**Sample:** Meta-analysis of 24 mortality studies in adults diagnosed with schizophrenia spectrum disorders who had received clozapine treatment with > 52 weeks of follow-up. **Outcome of interest:** Comparative mortality rates between clozapine and other antipsychotics.

continued overleaf

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Table 1.4 continued

Reference	Comments
Vermeulen et al., 2019 [23] cont'd	**Results:** For clozapine-treated patients, 1327 deaths were recorded during 217,691 patient-years of follow-up. Mortality rate ratios (mRR) were significantly lower in patients continuously treated with clozapine compared to other antipsychotics (mRR = 0.56, 95% CI 0.36–0.85). The mRR of studies including patients who ever used clozapine during follow-up compared to other antipsychotics was not significant (mRR = 0.74, 95% CI 0.38–1.45).

HR, hazard ratio.
*Not statistically significant.

published literature indicates that clozapine lowers the risk of premature mortality compared to other options for resistant schizophrenia.

Psychogenic Polydipsia

Primary polydipsia is a scenario of increased water intake occurring in the absence of impairment in water excretion. This can be distinguished from the secondary polydipsia seen with lithium-treated patients who increase water intake due to obligatory losses from nephrogenic diabetes insipidus. Both groups may have low urine osmolality, but the latter group maintains normal serum osmolality and serum sodium levels, while the primary polydipsia patient will suffer from severe hyponatremia and low serum osmolality during water binges [24]. The association of water intoxication and schizophrenia was reported in the pre-antipsychotic era, with a 1923 paper correlating increased water excretion with greater psychosis severity. By 1936 it was noted that excessive water intake occurred in approximately 25% of patients and was the most common metabolic abnormality in the severely mentally ill; moreover, it could be associated with life-threatening hyponatremia [24]. Modern prevalence data obtained over 5 years in a state hospital (1996–200) confirm that polydipsia continues to be present in at least 20% of chronic psychiatric inpatients [25]. The excessive drinking in primary polydipsia is not due to excessive thirst, but is motivated instead by delusions or psychic discomfort that is relieved by water binges [24].

Shortly after clozapine's approval in 1989, cases emerged in which water intoxication associated with schizophrenia was not addressed by typical antipsychotics, but which responded to clozapine. A 1996 case series of five state hospital patients with polydipsia who met Kane criteria reported that all were successfully discharged on clozapine and had no recurrence of polydipsia over 17 months of outpatient follow-up [26]. A subsequent 24-week open-label study

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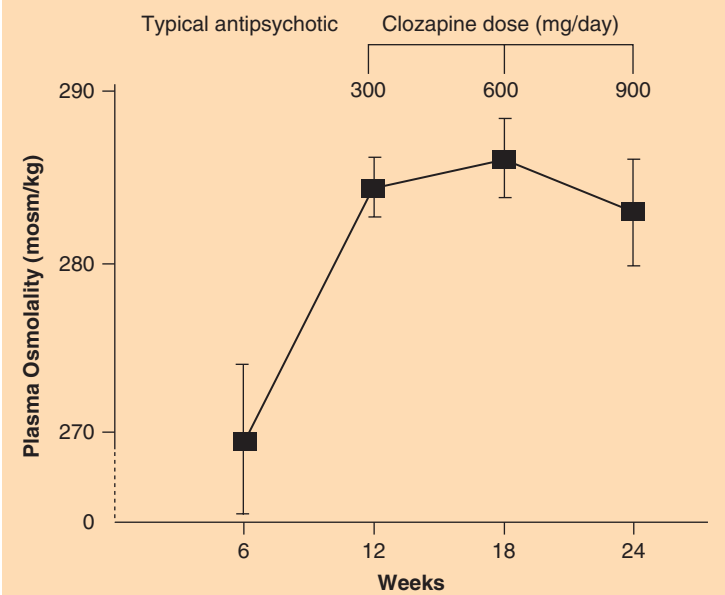
was performed in eight male schizophrenia patients with polydipsia to document longitudinal changes in urine and serum osmolality after starting clozapine [8]. The protocol involved 6 weeks with a typical antipsychotic (per Kane criterion 3), followed by sequential 6-week periods of clozapine at 300, 600 and then 900 mg/day (if tolerated). During treatment with typical antipsychotics both serum and urine osmolality remained grossly abnormal; however, on clozapine the mean plasma osmolality normalized, and rose on average by 15.2 mosm/kg (95% CI 5.5–25.0); moreover, this effect was evident at the dose of 300 mg/day of clozapine (see Figures 1.2 and 1.3) [8]. With ongoing clozapine titration, urine osmolality also normalized. No other prospective clozapine studies have emerged for polydipsia, but the

Figure 1.2. Mean plasma osmolality during 6 weeks of typical antipsychotic treatment followed by 6 weeks each of clozapine at 300, 600 and then 900 mg/day in schizophrenia patients with polydipsia.



(Adapted from: Canuso, C. M. and Goldman, M. B. (1999). Clozapine restores water balance in schizophrenic patients with polydipsia–hyponatremia syndrome. *Journal of Neuropsychiatry and Clinical Neuroscience*, 11, 86–90 [8].)

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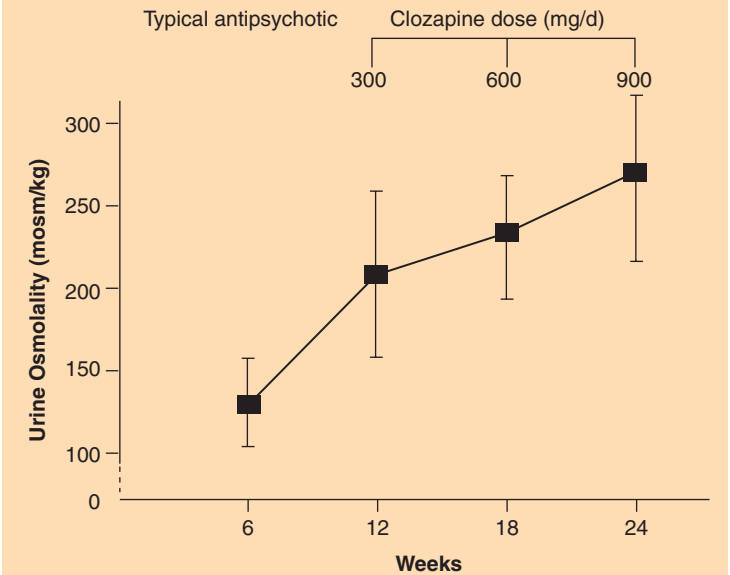
Figure 1.3. Mean urine osmolality during 6 weeks of typical antipsychotic treatment followed by 6 weeks each of clozapine at 300, 600 and then 900 mg/day in schizophrenia patients with polydipsia.



(Adapted from: Canuso, C. M. and Goldman, M. B. (1999). Clozapine restores water balance in schizophrenic patients with polydipsia–hyponatremia syndrome. *Journal of Neuropsychiatry and Clinical Neuroscience*, 11, 86–90 [8].)

accumulated literature is substantial enough that a 2010 comprehensive review of water imbalance issues in psychosis patients concluded that primary polydipsia generally appears resistant to antipsychotics except clozapine. Evidence-based treatment options for preventing water intoxication includes targeted fluid restriction, clozapine therapy, and removal of agents that may be causing hyponatremia (e.g. carbamazepine, valproate, sodium-wasting diuretics). The titration and therapeutic plasma levels for schizophrenia spectrum polydipsia patients are consistent with the use of clozapine for treatment-resistant schizophrenia.

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B Treatment-Intolerant Schizophrenia

Early in its clinical development, clozapine's extremely low rate of neurological adverse became apparent, leading to small trials in patients with tardive dyskinesia (TD), and for patients intolerant of D_2 antagonism due to akathisia, parkinsonism, acute dystonia or neuroleptic malignant syndrome (NMS) [27]. While use in TD patients was a focus of several studies, evidence for benefit in D_2 antagonist-intolerant patients is based on experience reported in case series where these patients were often included along with treatment-resistant individuals [28]. The conclusions from this case-based literature is that clozapine is unlikely to induce acute movement disorders, although there are a handful of NMS cases reported [29]. With respect to TD, both the efficacy outcomes and quality of prior studies led the American Academy of Neurology to state that the data were insufficient to support or refute use of clozapine for tardive syndromes [30]. Despite the abundance of case data, only three prospective studies involving a switch to clozapine for TD management were of sufficient quality to be reviewed: two were positive, one was not. A subsequent 2018 review found no further data to indicate that antipsychotic switching is an evidence-based practice for management of TD [31].

Since clozapine's reintroduction in 1989 the psychopharmacology landscape has changed in two ways: there are numerous options to high-potency typical antipsychotics, and there are three vesicular monoamine transporter type 2 (VMAT2) inhibitors available for TD treatment. The expanded group of atypical antipsychotics (including the D_2 partial agonists) provides a range of options for those with significant sensitivity to D_2 antagonism. Quetiapine has very low D_2 affinity and consequentially low rates of acute movement disorders, but enthusiasm for its use as a schizophrenia treatment has waned based on real-world effectiveness data associating quetiapine with higher rates of overall mortality [32], rehospitalization[17], any mental health event (suicide, hospitalization or emergency visit) or physical health event (death other than suicide, hospitalization or emergency visit for physical disorders) [16]. Although the pool of treatment-intolerant patients is smaller than when first-generation antipsychotics were the only available choices, these individuals do exist and should be offered clozapine. For stable TD patients who require ongoing antipsychotic therapy, the addition of a VMAT2 inhibitor is preferable to antipsychotic switching as the combination is well tolerated in severely mentally ill individuals on antipsychotic therapy (see Chapter 13). Clozapine should be considered if there are other ongoing sources of treatment intolerance (e.g. akathisia), or the patient meets clinical criteria for treatment resistance.

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C Suicidality

Conceptually, suicide and violence are separate domains of schizophrenia spectrum disorders that are not necessarily driven by psychotic thought processes, and thus respond incompletely to traditional antipsychotic therapy [33]. A review of suicidal acts among 10,118 schizophrenia patients participating in placebo-controlled clinical trials found that rates of suicide and attempted suicide did not differ significantly between the placebo-treated and drug-treated groups despite greater symptom reduction for the latter [34]. Patients with schizophrenia spectrum disorders have ninefold higher rates of unnatural causes of death (suicide, violent accidents) compared to the general population, with suicide risk especially prominent in the first 5 years after diagnosis [35,36]. Death from suicide comprises 30% of all causes of mortality in studies of new-onset schizophrenia patients, but wanes over ensuing decades. The estimated lifetime risk of death from suicide is 4.9% in patients with schizophrenia [36].

The impact of clozapine on suicidality was first noticed in treatment-resistant schizophrenia patients, but the antisuicide effects were later seen in those without treatment resistance, and in bipolar disorder patients [37–39]. From these observations the foundation was laid for a large international trial to examine clozapine's comparative efficacy vs. olanzapine in a nonresistant schizophrenia population. The International Suicide Prevention Trial (InterSePT) enrolled 980 patients at high risk for suicide due to prior attempts or current symptoms, with 24 months of follow-up (see Figure 1.4) [40]. In this cohort of schizophrenia patients who were not treatment-resistant, clozapine's superior impact on suicidality was clearly independent of the reduction in psychotic symptoms, as both clozapine and olanzapine had comparable improvements in total Positive and Negative Syndrome Scale (PANSS) scores. This principle will be echoed in data supporting clozapine's effect on aggression: *the reduction in suicidality and violence is independent of clozapine's antipsychotic effect.* The InterSePT study resulted in an indication for reducing risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder "who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state" [41]. Naturalistic data summarized in Table 1.4 substantiate the findings from InterSePT: clozapine treatment is associated with a reduction of 66–80% in deaths by suicide or other unnatural causes, and a 36% lower rate of self-harm compared with nonclozapine antipsychotics.

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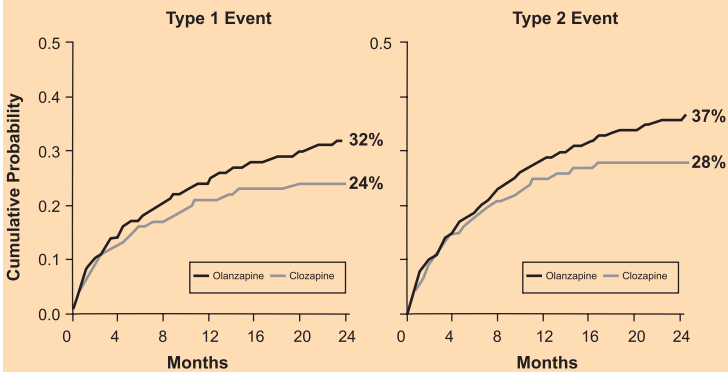
Figure 1.4. Time to suicidal events in the InterSePT study.



HR, hazard ratio. Type 1 Event: Significant suicide attempt or hospitalization due to imminent suicide risk. Type 2 Event: Worsening suicidality.
(Adapted from: Meltzer, H. Y., Alphs, L., Green, A. I., et al. (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Archives of General Psychiatry*, 60, 82–91 [40].)

Box 1.2 Important Conclusions from the 24-Month Prospective, Randomized International Suicide Prevention Trial (InterSePT) [40]

1. In this group of 980 schizophrenia patients who were not treatment-resistant but at high risk for suicide, clozapine and olanzapine had comparable reductions in symptom ratings (PANSS total score).
2. Despite equivalent reduction in psychosis symptoms, clozapine was superior to olanzapine for overall suicidal behavior (HR = 0.76; 95% CI 0.58–0.97). Specifically, *fewer clozapine-treated patients*:
   - attempted suicide
   - required hospitalizations or needed rescue interventions to prevent suicide
   - required concomitant treatment with antidepressants or anxiolytics/hypnotics
3. Clozapine delayed the time to occurrence of suicidal events compared to olanzapine treatment, and this effect was increasingly more significant over time for both Type 1 and Type 2 events as defined below:

Type 1 Event: Significant suicide attempt or hospitalization due to imminent suicide risk

Type 2 Event: Worsening suicidality (as indicated by a rating of “much worse” or “very much worse” from baseline on the Clinical Global Impression Severity of Suicidality scale)

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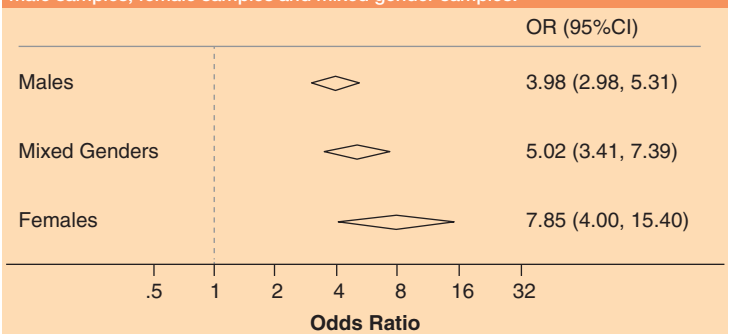
D Violence and Aggression

The association between psychosis and violence has been noted for over a century, but only in recent decades have there been systematic attempts to understand the intrinsic neurobiological factors and extrinsic factors (e.g. substance use) that moderate this risk. Quantifying this risk has been challenging because violence or aggression can include a spectrum of behaviors from verbal threats to physical violence or murder. The lack of consensus definitions for the term "violence" in research papers leads to a range of reported rates [42]. Despite these limitations, a comprehensive 2009 review noted that violence risk is increased for both male and female schizophrenia patients, and that substance use further increases risk of violence 3.7- to 4.2-fold in this population compared to psychosis patients without substance use (see Figure 1.5) [43,44].

Aggression in undermedicated or untreated schizophrenia patients is approached with standard pharmacological interventions including antipsychotics alone or with mood stabilizers (if there is a bipolar diathesis) [33]. The more problematic clinical scenario revolves around the type of schizophrenia patient encountered

Figure 1.5. Risk estimates for violence in schizophrenia and other psychoses for male samples, female samples and mixed gender samples.



OR, Odds Ratio; CI, Confidence Interval.
(Adapted from: Fazel, S., Gulati, G., Linsell, L., et al. (2009). Schizophrenia and violence: Systematic review and meta-analysis. *PLoS Medicine*, 6, e1000120 [43].)

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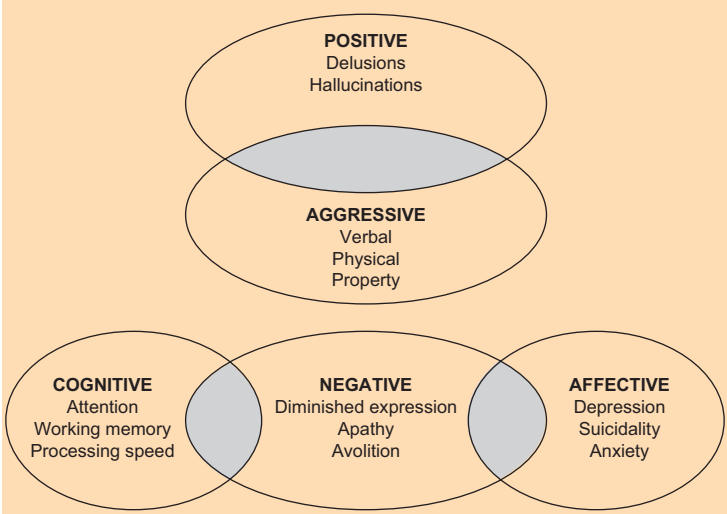
in psychiatric inpatient and forensic settings who remains persistently aggressive despite antipsychotic treatment. In addressing the persistently violent schizophrenia spectrum patient, one must first categorize the nature of the aggression. The most robust and empirically validated classification method was developed within the New York State Hospital system based on reviewed videotaped assaults supplemented with assailant and victim interviews to determine the motivation for each violent act. These detailed assessments led the authors to conclude that three categories could be used to define aggressive acts: psychotic, impulsive, and predatory (also called organized or instrumental) [33]. The latter group comprises intentional acts for secondary gain (e.g. theft, intimidation), and requires a custodial solution, not pharmacotherapy. Psychotic violence is due to persistent delusions or hallucinations that drive behaviors, while impulsive acts involve inappropriate responses to real-world stimuli. A classic example of impulsive violence is a patient who assaults a peer after being gently bumped in a line despite the innocuous nature of the contact and the fact that the assault will have repercussions for

Figure 1.6. Violence is a separate symptom dimension of schizophrenia.



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the assailant (e.g. legal, loss of privileges, etc.). Utilizing this classification, there are two core concepts that underlie treatment of ongoing violence in medicated schizophrenia patients:

a. Among persistently aggressive forensic schizophrenia inpatients the most common type of assault is impulsive (54%), followed by organized (29%) and psychotic (17%) [45].
b. Impulsive violence/aggression is a separate symptom dimension of schizophrenia that may not respond to nonclozapine antipsychotics (see Figure 1.6) [33].

The initial approach to any violent patient requires the clinician to classify the nature of the violence. That motivated by delusions or hallucinations involves optimization of antipsychotic treatment, and use of clozapine in those who are treatment-resistant. For those who are impulsive, further antipsychotic titration is appropriate if there are no dose-limiting adverse effects (e.g. akathisia, parkinsonism). In schizophrenia patients who continue to be impulsively violent despite maximal use of nonclozapine antipsychotics, clozapine is the preferred agent, and its anti-aggressive property in these individuals is independent of its impact on psychotic symptoms. Evidence for this assertion comes from studies summarized in Table 1.5 [46]. The most rigorous study design was a randomized, double-blind, parallel-group, 12-week trial specifically for physically assaultive New York State Hospital patients with schizophrenia or schizoaffective disorder [47]. At study end there were nonsignificant numerical changes in PANSS total scores across all three drug groups, but clozapine significantly reduced verbal, physical and total aggression scores compared to haloperidol or olanzapine. Clozapine's effect was more pronounced in those with cognitive dysfunction, despite the fact that poor executive function at study baseline predicted higher levels of aggression (see Figure 1.7) [48].

Further evidence that clozapine's anti-aggression effect is independent of its antipsychotic properties includes a small case series of clozapine therapy for impulsive aggression among nonpsychotic patients with antisocial personality disorders. Not only did clozapine significantly decrease rates of impulsive aggression and violence in this cohort, it did so at a mean plasma level of 171 ng/ml, well below the 350 ng/ml threshold used to manage treatment-resistant schizophrenia [49]. A 2018 review outlines the challenges to prescribing clozapine in forensic settings,

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Table 1.5 Summary of randomized studies of clozapine for aggression in schizophrenia.

Reference	Comments
Niskanen et al., 1974 [73]	**Sample:** Randomized, double-blind, 40-day trial of clozapine vs. chlorpromazine in 48 patients with chronic schizophrenia, 75% of whom were experiencing acute symptoms or exacerbation of chronic symptoms. **Outcomes of interest:** Change in BPRS score. **Results:** Improvements in tension, hostility and excitement were seen in the clozapine group compared to baseline, with no between-group differences in BPRS scores.
Chow et al., 1996 [74]	**Sample:** Open-label, 14-week randomized trial in aggressive inpatients with schizophrenia (n = 12), schizoaffective disorder (n = 2) or dementia with psychotic features (n = 1). Subjects were randomized to clozapine or remaining on their current antipsychotic. **Outcomes of interest:** Change in total score on the MOAS. Secondary outcome was change in PANSS total score. **Results:** Aggression scores improved in the clozapine group at week 10 and at week 14 compared to baseline. PANSS total scores did not improve for either group.
Citrome et al., 2001 [75] Volavka et al., 2002 [76] Volavka et al., 2004 [77]	**Sample:** Randomized, double-blind, 14-week trial of clozapine, olanzapine, risperidone or haloperidol in 157 adult inpatients (ages 18–60) with total PANSS ≥ 60, suboptimal response to treatment and poor functioning over the prior 2 years. **Outcome of interest:** Change in PANSS total score, and total aggression severity score. **Results:** Atypical antipsychotics were superior to haloperidol for symptom reduction, and clozapine was superior to haloperidol in reducing the number and severity of aggressive incidents. Risperidone and olanzapine had less antipsychotic efficacy in aggressive patients; the opposite was true for clozapine.
Krakowski et al., 2006 [47]	**Sample:** Randomized, double-blind, parallel-group, 12-week trial. Subjects were physically assaultive inpatients with schizophrenia or schizoaffective disorder in New York State psychiatric facilities randomly assigned to clozapine (n = 37), olanzapine (n = 37) or haloperidol (n = 36). **Outcome of interest:** Changes in total score on the MOAS-30, and the three MOAS-30 subscales (physical aggression against other people, verbal aggression, and physical aggression against objects). Nursing staff reported all behaviors on a monitoring form with 30- to 60-minute intervals. Research personnel interviewed the nursing staff after each event. **Results:** There were no significant between-group differences for mean change in PANSS total score. Clozapine was superior to olanzapine for change in MOAS-30, for physical aggression against other people, and for verbal aggression. Clozapine was superior to haloperidol for MOAS-30 total score, and for physical aggression against other people, verbal aggression, and physical aggression against objects.

BPRS,Brief Psychiatric Rating Scale; MOAS, Modified Overt Aggression Scale; PANSS, Positive and Negative Syndrome Scale

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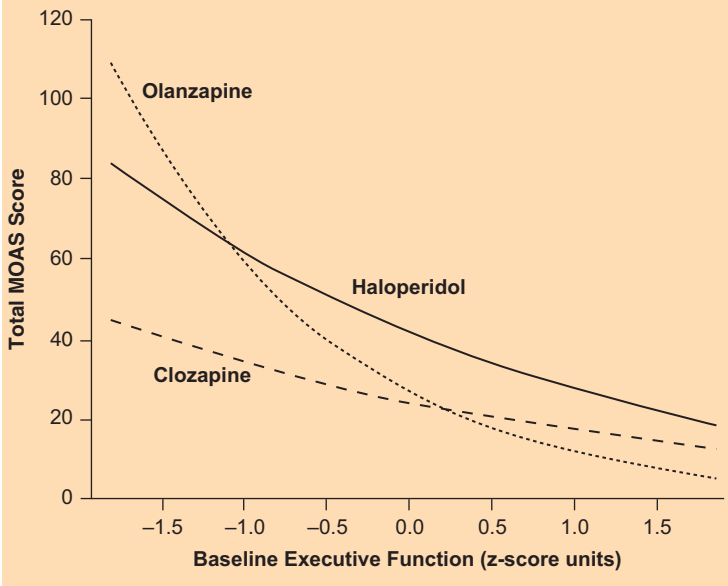
Figure 1.7. Clozapine's superiority for aggression compared to olanzapine and haloperidol among schizophrenia patients with cognitive dysfunction.



MOAS, Modified Overt Aggression Scale.
(Adapted from: Krakowski, M. I. and Czobor, P. (2012). Executive function predicts response to antiaggression treatment in schizophrenia: A randomized controlled trial. *Journal of Clinical Psychiatry*, 73, 74–80 [48].)

including the lack of an intramuscular formulation in most countries, and the greater attention required for management of adverse effects. Nonetheless, the authors note the cost-effectiveness of clozapine treatment as an important part of any strategy to manage aggressive, severely mentally ill patients in health-care and criminal justice systems [50].

E Treatment-Resistant Mania

The value of clozapine for treatment-resistant mania was noted in case reports as early as 1977 [51], but not until 1994 was a trial conducted in patients who met a standardized definition of treatment resistance: documented response failure or

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intolerance to lithium, an anticonvulsant, and at least two typical antipsychotics. All subjects ($n = 25$) in that 13-week open-label trial met DSM-IIIR criteria for the manic phase of bipolar disorder or schizoaffective disorder, bipolar type [52]. At study endpoint, 72% of patients demonstrated at least 50% decrease in the Young Mania Rating Scale (YMRS) score. A subsequent 1-year trial with 38 treatment-resistant patients meeting DSM-IV criteria for the manic phase of schizoaffective or bipolar disorder randomly assigned subjects to adjunctive open-label clozapine ($n = 19$) or treatment as usual (TAU) ($n = 19$), with monthly ratings of mood and psychosis symptoms [53]. Significant between-group differences were found in scores on all rating scales except the Hamilton Depression scale, and medication use decreased significantly in the clozapine group. Importantly, patients with nonpsychotic bipolar I disorder randomized to clozapine exhibited similar improvement in mania symptoms as did the entire clozapine-treated group, providing evidence that clozapine's antimanic effect is independent of the antipsychotic effect [53]. There were differences in mean clozapine doses between those with schizophrenia spectrum disorders (623 mg/day) and nonpsychotic bipolar I patients (234 mg/day). A subsequent 12-week trial of 22 bipolar I patients with mania and psychotic features noted a mean dose among completers of 334 mg/day [54]. Double-blind, placebo controlled adjunctive studies do not exist, but there are case series for use in rapid cycling bipolar disorder [55].

Real-world data support the conclusions of open-label studies that clozapine is effective for treatment-resistant mania in bipolar I patients. Using the Denmark national database for the years 1996–2007, investigators examined outcomes in bipolar disorder patients started on clozapine ($n = 326$) specifically excluding those with a schizophrenia spectrum disorder. The study used a mirror image design to look at comparative hospital days, number of psychiatric admissions, and medication usage for the 2 years before and 2 years after starting clozapine [56]. After a mean follow-up of 544 ± 280 days, the number of hospital bed days decreased by 80% from 178 to 35 ($p < 0.001$), and the mean number of admissions decreased by 37.5% from 3.2 to 2.0 ($p < 0.001$). Overall, 74% had reduced bed days and 40% were not admitted at all while on clozapine. Using defined daily doses (DDD), the number of psychotropic medications decreased by 13% from 4.5 to 3.9 DDD ($p = 0.045$). Nonpsychiatric hospital visits for intentional self-harm or medication overdose also decreased significantly from 8.3% to 3.1% ($p = 0.004$). The mean clozapine dose at the end of follow-up was 307.4 mg/day. After 1 year of clozapine exposure, use of medications to manage nonpsychiatric

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medical conditions did not increase. As noted in schizophrenia, clozapine is only effective for mania when patients adhere to treatment. Bipolar patients deemed "irregular" clozapine users in a Taiwan analysis by virtue of low medication possession ratios had twofold higher adjusted risk for emergency room visits, and 2.5 times greater risk for hospitalizations compared to more adherent clozapine patients [57].

Box 1.3 Essential Facts about Use of Clozapine For Treatment-Resistant Mania

1. Adjunctive clozapine is equally effective in treatment-resistant nonpsychotic bipolar patients and those with a diagnosis of schizoaffective disorder, bipolar type.
2. Use of clozapine is associated with reduced hospital admissions, number of hospital days, hospital visits for self-harm or intentional overdose, and total psychotropic medication use.
3. Mean endpoint doses for bipolar I patients in long-term studies of 1 year or more range from 234 to 305 mg/day [53,56]. Higher doses (and plasma levels) typical of schizophrenia spectrum disorders are usually needed for schizoaffective disorder, bipolar type patients. There is one study of rapid clozapine titration among treatment-resistant bipolar disorder inpatients, but this reduced time to discharge readiness by less than 4 days. In a forced titration study that advanced clozapine by 25 mg/day to a target dose of 550 mg/day (if tolerated), only 14 of 22 manic bipolar I patients managed to complete the 12-week trial [54].

F Parkinson's Disease Psychosis (PDP)

Parkinson's disease (PD) is a neurodegenerative disorder related to the neuronal accumulation of alpha-synuclein in histologically distinct complexes called Lewy bodies. The worldwide prevalence of PD is estimated at > 7 million, of which more than 50% will develop symptoms of Parkinson's disease psychosis (PDP). The prevalence of PDP increases to 75% of patients in those with PD and related dementia. In 2007 a consensus definition for PDP was elaborated that included the existence of hallucinations, delusions, illusions or false sense of presence for at least 1 month in a patient previously diagnosed with PD and in whom other etiologies have been ruled out (e.g. delirium) [58]. The development of PDP is associated with increased caregiver burden, increased likelihood of nursing home placement, and is associated with increased mortality [59].

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For most of the twentieth century, PD was viewed primarily as a motor disease related to loss of dopamine neurons in the nigrostriatal pathway, but PD is now recognized as a multisystem disease associated with cognitive impairment related to loss of cholinergic neurons, depression due to loss of noradrenergic neurons, autonomic and other nonmotor symptoms [60]. In prior decades PDP was often referred to as levodopa psychosis under the belief that excessive dopaminergic stimulation from dopamine agonist treatment was the principal underlying cause. It is now understood that the pathophysiology of PDP is due to loss of serotonergic midbrain dorsal raphe neurons from the accumulated Lewy body burden in these cells. The loss of this serotonin signal results in upregulation and supersensitivity of postsynaptic $5HT_{2A}$ receptors, a finding confirmed by neuroimaging of PD patients with and without psychosis [61]. That increased stimulation of $5HT_{2A}$ receptors can induce psychotic symptoms has been known for decades based on elucidation of common mechanisms among hallucinogens such as psilocybin and lysergic acid diethylamide.

The therapeutic dilemma in treating PDP relates to the profound loss of dopamine neurons in the dorsal striatum, and the inability to tolerate antipsychotics that possess moderate D_2 affinity without significant worsening of motor symptoms. Recognition that clozapine was associated with extremely low risk for drug-induced parkinsonism led to a 1990 study exploring its tolerability in six PDP patients at doses ranging from 75 to 250 mg/day (mean 170.8 mg/day) [62]. This early study noted a 50% response rate, but 50% also experienced worsening motor symptoms at those doses. These findings informed the design of the two seminal PDP studies published in 1999, one from a French group and the second from a US consortium. Each study was a double-blind, placebo-controlled 4-week trial, and both enrolled a total of 60 subjects. Based on high rates of motoric worsening in the 1990 study, the starting clozapine dose in each trial was 6.25 mg/day, with titration every 3–4 days based on response and tolerability. In the French study mean endpoint clozapine dose was 36 mg/day, while it was 24.7 mg/day in the US-based **Psychosis and Clozapine in the treatment of Parkinsonism (PSYCLOPS**) trial [63,64]. At these low doses, clozapine was significantly more effective than placebo in both trials, and with large effect sizes; moreover, there was no exacerbation of parkinsonism in the PSYCLOPS study, while 22% of patients in the French trial noted mild or transient worsening of parkinsonism, although no patient discontinued the study for this reason. Results from the 12-week PSYCLOPS extension study ($n = 53$)

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confirmed the efficacy of low-dose clozapine for PDP (mean 28.8 mg/day), again without worsening of underlying Parkinson's disease symptoms as noted by ratings of motor function or need for higher doses of dopamine agonist medications [65]. Recent naturalistic data are consistent with the clinical trials findings. A retrospective review of 36 PDP patients treated at one center (mean age 68 years) noted that 33% had complete response, and 33% a partial response to clozapine [66]. Highlighting the practical issues involved with clozapine administration, the overall retention rate on clozapine was only 41%, and the most common reasons for discontinuation were frequent blood testing (28%), refusal of medical staff to continue clozapine after nursing home placement (11%) and neutropenia (8%). Only 2.8% stopped clozapine due to worsening motor symptoms, and a similar proportion discontinued treatment due to orthostasis or delirium (2.8% for each). The possible benefit of clozapine for levodopa-induced dyskinesias (LID) was later studied in 50 PD patients without psychosis in a 10-week, double-blind, placebo-controlled, multicenter trial. The principal outcome was change in the LID "on" time (hours per day). At a mean clozapine dose of 39.4 mg/day, clozapine treatment was associated with reduction in the duration of "on" periods from 5.68 h/day to 3.98 h/day, while the placebo group slightly worsened from 4.54 h/day to 5.28 h/day [67].

Over the ensuing decade other atypical antipsychotics have been used in PDP patients with results primarily reported in case series. Most have proved ineffective and were associated with significant motoric worsening (olanzapine, risperidone, ziprasidone, aripiprazole) [68]. Only olanzapine and quetiapine were examined in double-blind studies as summarized in Table 1.6. In all trials olanzapine was ineffective, and in the largest studies olanzapine exacerbated parkinsonian symptoms. Quetiapine was generally ineffective, but did not induce motoric adverse effects. Despite widespread use for PDP, a recent meta-analysis concluded that: "Given the randomized controlled trial-derived evidence, quetiapine should not be used in this indication, unless further studies have clarified this issue" [69]. Concerns over quetiapine were further heightened by results of a large retrospective study exploring 180-day mortality rates in 7877 PD patients starting antipsychotic treatment and 7877 PD patients who did not take an antipsychotic matched for age, sex, race, year of treatment, presence and duration of dementia, duration of PD, delirium, medical comorbidity, and hospitalization. In this study, mortality was increased by a factor of 2.16 for quetiapine [70]. Unfortunately, the number of clozapine cases was too small to analyze separately.

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Table 1.6 Summary of double-blind studies for Parkinson's disease psychosis [68].

Reference	Medication(*N*)	Effect on psychosis symptoms	Effect on motor symptoms
The French Clozapine Parkinson Study Group 1999 [64]	Clozapine (*n* = 60)	+++	0
Parkinson Study Group 1999 [63]	Clozapine (*n* = 60)	+++	0
Goetz et al., 2000 [78]	Olanzapine (*n* = 15)	0	–
Breier et al., 2002 [79]	Olanzapine (*n* = 160)	0	–
Ondo et al., 2002 [30]	Olanzapine (*n* = 30)	0	0
Ondo et al., 2005 [31]	Quetiapine (*n* = 31)	0	0
Rabey et al., 2007 [82]	Quetiapine (*n* = 58)	0	0
Shotbolt et al., 2009 [83]	Quetiapine (*n* = 24)	0	0
Fernandez et al., 2009 [34]	Quetiapine (*n* = 16)	+	0
Friedman et al., 2010 [85]	Pimavanserin (*n* = 298)	+	0
Cummings et al., 2014 [59]	Pimavanserin (*n* = 199)	++	0

Despite its efficacy data, a limiting factor in clozapine use for PDP relates to the mandatory hematological monitoring, as a weekly laboratory trip can prove daunting for a patient group comprised of older individuals with limited mobility. To obviate this issue, researchers have sought to harness clozapine's effectiveness in a molecule that does not require laboratory monitoring. At the low doses used for PDP one of clozapine's most prominent receptor actions is at $5HT_{2A}$, and this is likely the primary site of action based on the known pathophysiology of this disorder. This insight led to development of the potent selective $5HT_{2A}$ antagonist pimavanserin for PDP (Ki 0.087 nM), with US FDA approval granted in 2016 [59]. Pimavanserin lacks affinity for dopaminergic, cholinergic, alpha-adrenergic and histaminergic receptors, and in clinical trials had no impact on ratings of motor function. While pimavanserin is a promising development in PDP treatment, it is currently only available in the US, so clozapine remains the mainstay of PDP management worldwide, and for those who fail to respond to pimavanserin.

Box 1.4 Essential Facts about Use of Clozapine for Parkinson's Disease Psychosis

1. The initial starting dose is 6.25 mg PO QHS (*quaque hora somni* – every night at bedtime). The clozapine dose can be advanced in 6.25 mg increments as needed every 3–4 days, with most patients responding at doses < 50 mg/day. The mean doses reported in clinical studies range from 25 to 36 mg/day.
2. Routine hematological monitoring must be performed.
3. While generally well tolerated, sedation, orthostasis, worsening motor symptoms and constipation have been reported.

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Summary Points

a. Clozapine is the only antipsychotic with compelling efficacy data in treatment-resistant schizophrenia, and in schizophrenia spectrum patients with psychogenic polydipsia, suicidality or aggression that does not respond to other antipsychotics.

b. Clozapine's effectiveness for suicidality and aggression is independent of the antipsychotic effect.

c. In real-world use clozapine reduces hospitalization rates, and is associated with lower mortality rates from unnatural causes (suicide, accidents) and from natural causes.

d. Clozapine's efficacy as an adjunctive agent for treatment-resistant mania is also independent of the antipsychotic effect.

e. Clozapine is a mainstay for the treatment of PDP, although pimavanserin is approved in the US for this indication. Quetiapine appears ineffective in most PDP trials and is associated with a 2.16-fold increased mortality risk over 180 days compared to PD patients on no antipsychotic.

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