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# Clozapine Across Treatment-Resistant Symptom Dimensions: A Conceptual Review and Transdiagnostic Rationale for Child and Adolescent Psychiatry

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## Abstract

Clozapine is the most effective antipsychotic for treatment-resistant schizophrenia, yet in children and adolescents it remains off-label and underused, constrained by safety concerns and scarce pediatric-specific evidence. Its benefits may extend beyond any single diagnostic category to severe, treatment-resistant dimensions of psychopathology that recur across diagnoses. This review traces clozapine's history in youth, synthesizes the current evidence, and organizes it by domains of treatment resistance: psychosis, aggression, affective symptoms, suicidality and self-directed harm, and catatonia, with sections on real-world outcomes, clinical management, and safety. Randomized controlled data are confined to treatment-resistant early-onset schizophrenia and to one small trial in conduct disorder, with the first prospective open-label trial now available in autistic youth. Elsewhere the evidence is observational and of lower certainty, although convergent for aggression, suicidality, mood, and catatonia. The strongest transdiagnostic evidence is register-based and within-individual, drawn from cohorts aged 16 years and older, and spans psychotic and affective disorders; the pediatric gap concerns study design as well as sample size. Because pharmacovigilance data show that mortality is not concentrated in the hematological domain, safe use requires surveillance beyond blood counts, therapeutic drug monitoring, and safeguards over drug supply when suicide risk is present. Viewing clozapine as a treatment option defined by symptom severity and refractoriness may support rational use in severely ill youth, but the proposal remains preliminary: a conceptual framework that requires prospective, dimensionally designed pediatric studies. Clozapine's potential transdiagnostic anti-suicidal effect merits priority investigation, given that suicide is a leading cause of death in adolescence.

**Keywords:** clozapine; early-onset schizophrenia; treatment resistance; transdiagnostic approach; aggression; suicidality; pediatric psychopharmacology; pharmacovigilance; off-label use

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## 1. Introduction

Clozapine is increasingly recognized as effective across a range of treatment-resistant neuropsychiatric conditions, extending beyond its established role as the gold standard for treatment-resistant schizophrenia-spectrum disorders [1,2]. Yet despite consistent evidence of its superior efficacy and a global increase in clozapine use, it remains underutilized worldwide: many eligible patients are never offered the treatment, and others face substantial delays before initiation [3–5]. Long regarded as a last-resort intervention because of safety concerns, clozapine has gradually been recognized for its unusual pharmacological profile [6] and its ability to target severe symptom domains, such as suicidality [7], that may transcend the traditional categories of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD). Decades after its synthesis and the introduction of numerous newer atypical antipsychotics, no other agent has replicated its breadth of efficacy [8], and it retains a singular place in the management of severe, treatment-resistant psychopathology. In child and adolescent mental health care, mirroring adult practice, its off-label use has extended beyond early-onset psychotic disorders to other severe, treatment-resistant presentations, particularly those marked by high aggression, affective dysregulation, and impulsivity that resist conventional pharmacological and non-pharmacological strategies and cause marked functional impairment, patient suffering, and caregiver burden [9,10].

In parallel, contemporary psychiatry has moved toward transdiagnostic models that emphasize dimensions of psychopathology over strict diagnostic categories. This shift reflects growing recognition of the limitations of categorical diagnoses, including excessive comorbidity, within-disorder heterogeneity, and arbitrary diagnostic thresholds that reduce their utility in both research and clinical practice [11]. These limitations are especially relevant in pediatric populations, whose presentations are often heterogeneous, developmentally dynamic, and poorly captured by DSM-based entities [12]. From this standpoint, treatments can also be conceptualized transdiagnostically by their capacity to modulate shared symptom dimensions across diagnostic boundaries. This is illustrated by the Supportive Parenting for Anxious Childhood Emotions program, a parent-based intervention that targets family accommodation as a shared maintaining mechanism and is effective across distinct pediatric psychiatric conditions (i.e., anxiety and obsessive-compulsive disorders) [13]. Pharmacologically, clozapine is a paradigmatic example: its mechanisms extend well beyond the dopaminergic and serotonergic receptor binding that characterizes most antipsychotics, encompassing cholinergic, GABAergic, noradrenergic, and glutamatergic modulation, while preclinical data further implicate non-classical routes such as immunomodulatory, anti-inflammatory, and neuroplastic effects [6,8,14,15]. The clinical relevance of these non-classical effects, however, remains limited and correlational. Although a complete account of its therapeutic properties remains elusive, this multimodal neurobiological activity may partly explain clozapine's utility across a wide spectrum of severe, treatment-resistant symptom dimensions, which may not be restricted to adulthood.

These observations raise the question of whether clozapine might be conceptualized as a transdiagnostic therapeutic agent in child and adolescent psychiatry, even as its clinical utility and evidence base within this framework remain to be established. While such a reframing invites a more dimensional, mechanism-informed view of treatment, translating it into practice faces substantial obstacles, chief among them safety and monitoring barriers that may keep youth with persistent psychopathology from an intervention that could benefit them, compounded by the scarcity of pediatric-specific data on clozapine's clinical management, pharmacokinetics, and safety [10,16]. Because treatment resistance has an operational definition only for psychosis, we also make explicit how the construct was defined in the studies reviewed and where it remains undefined.

This review examines the emerging role of clozapine in child and adolescent psychiatry through a transdiagnostic lens, a perspective still underexplored in the pediatric literature. We synthesize clozapine's historical evolution in the field, its potential use across specific symptom dimensions where treatment resistance manifests in youth, and the clinical challenges of clozapine treatment in pediatric populations, with particular attention to safety. Recognizing the incipient nature of the current evidence, we propose a novel conceptual framework for understanding this role. By reframing its application beyond conventional diagnostic silos, we seek to lay the theoretical groundwork for future transdiagnostic research and, ultimately, more individualized strategies for youth and families facing seemingly intractable psychopathology.

## 2. Methods

This work was conceived as a conceptual narrative review, a design suited to synthesizing a heterogeneous, still-incipient body of evidence and to articulating the transdiagnostic framework proposed herein. We searched PubMed/MEDLINE and Embase from inception to March 2026, combining controlled vocabulary and free-text terms across three blocks: the drug ("clozapine"); the developmental population ("child", "adolescent", "pediatric", "youth", "early-onset"); and the clinical context ("treatment-resistant", "refractory", "transdiagnostic", and specific symptom dimensions such as aggression, suicidality, and psychosis). Searches were limited to English-language publications, and the reference lists of key articles were manually screened. Non-English primary sources, notably the early German-language trials, were therefore accessed only through English-language secondary appraisals. A second, unstructured stage followed: publications appearing after the formal search date were identified through journal table-of-contents alerts, database alerts, and the reference lists of newly published work, and were incorporated up to manuscript completion in August 2026. This surveillance phase was not subject to formal screening and, by its nature, may favor recent and positive reports. Records were screened by two authors (A.L.S.T.d.R. and L.d.O.C.) and selected for thematic relevance, prioritizing clinical trials, observational studies, case series and reports, systematic reviews, and practice guidelines addressing the efficacy, effectiveness, or safety of clozapine in youth; disagreements were resolved by discussion, and residual doubts were referred to the senior author (A.S.G.-M.). Because records were not logged at the identification and screening stages, the number of records screened and retained cannot be reported.

Given the limited pediatric-specific data, relevant adult studies were included to provide historical context, to allow cautious extrapolation, or when young people formed part of the study sample. Two studies by the present authors [17,18] were included under the same criteria as the rest of the literature and are reported with their design limitations stated explicitly. The retrieved evidence was organized around symptom dimensions rather than discrete diagnostic categories. Because the aim was evidence mapping and conceptual synthesis rather than exhaustive effect estimation, systematic-review procedures such as protocol registration, record logging, and risk-of-bias appraisal were not applied. Generative AI (Claude Opus 5, Anthropic, San Francisco, CA, USA, accessed July–October 2026) was used to (i) edit the manuscript's language for clarity and phrasing; (ii) write code that generated initial PowerPoint drafts of Figures 1–3, whose content was specified by the authors and which the authors subsequently edited in PowerPoint; (iii) draft the initial layout of Table 1; and (iv) prepare submission materials. The authors conducted the literature search and study selection and verified all cited sources against the original publications. Representative prompts used during this AI-assisted work are provided in Supplementary Materials (Document S1).

## 3. History of Clozapine in Child and Adolescent Psychiatry: From Treatment-Resistant Psychosis Toward a Transdiagnostic Utility

Clozapine was synthesized in 1958 in Switzerland by Wander AG during research on novel tricyclic compounds initially intended for antidepressant development. Early studies showed robust antipsychotic efficacy without the catalepsy and motor rigidity of the first-generation agents of the era, an unprecedented dissociation that distinguished clozapine from contemporaneous dopamine-blocking drugs and anticipated its later recognition as the prototype of the atypical antipsychotics. The drug was approved in Austria and Switzerland in 1972 and in West Germany in 1974, reaching Finland in 1975—the year in which Finnish pharmacovigilance reports described 18 cases of agranulocytosis and 8 deaths among approximately 2000 patients. Sandoz considered withdrawing clozapine, and United States (US) development was halted in 1976, but the drug remained available in German-speaking Europe through the intervention of Hippius and other central European investigators [19], an episode and its regulatory aftermath traced in detail elsewhere [20]. The ensuing market withdrawals and regulatory restrictions durably shaped the drug's safety perception, tying it to hematological risk and fostering a risk-averse paradigm that still underlies its persistent global underutilization, with most patients with treatment-resistant schizophrenia (TRS) never receiving the treatment of choice [3,21], even though barriers and facilitating factors have been extensively investigated [22].

The drug's status changed decisively with John M. Kane's landmark 1988 trial in 268 patients [23], which demonstrated superiority over chlorpromazine in TRS and led to US Food and Drug Administration (FDA) approval in 1989 under mandatory hematological monitoring, later operationalized as the Clozapine Risk Evaluation and Mitigation Strategy (REMS) in 2015 [21]. This high-surveillance model has since been relaxed, with the FDA discontinuing mandatory REMS participation in 2025 and the European Medicines Agency issuing revised recommendations that maintain structured but progressively less frequent surveillance [24,25]. The transdiagnostic signal, however, long predates this modern literature. The registration-era trials published in German, absent from PubMed and largely overlooked since, were accessible solely through the critical review by Ferrea et al. [19]. These early studies showed that patients with mania were already being included, with one trial proposing anti-aggressive effects across diagnoses at doses up to 75 mg/day in a mixed sample of 42 patients with intellectual disability, personality disorders, or schizophrenia [19]. Subsequent research broadened clozapine's relevance well beyond acute psychosis: it showed anti-suicidal effects in schizophrenia and schizoaffective disorder [26] and lower rates of substance use among individuals with psychotic disorders [27]. Clinical experience and additional research have gradually expanded its off-label utilization to include mood disorders, borderline personality disorder, Parkinson's disease psychosis, and pathological aggression [28–30]. More recently, systematic reviews have shown that several of its effects, notably on suicidality and aggression, recur across diverse conditions [7,31], suggesting that key therapeutic properties transcend conventional diagnostic boundaries.

Figure 1 sets these adult population milestones against the pediatric evidence that developed in parallel. Renewed clinical confidence drove the extension of clozapine to early-onset psychotic disorders during the 1990s. Because early age of onset is itself a recognized risk factor for treatment resistance, and because roughly a quarter of patients with first-episode schizophrenia develop treatment-resistant illness [32], this population represented a particularly compelling target for clozapine. The earliest pediatric evidence came from small case series published between 1992 and 1995 [33–37] and an open-label trial by Frazier et al. [38], which consistently reported marked improvement and low extrapyramidal liability in children and adolescents with schizophrenia. These observations were reinforced by randomized controlled trials (RCTs) in early-onset schizophrenia (EOS)

supported by the National Institute of Mental Health, most notably Kumra et al.'s double-blind comparison of clozapine with haloperidol in 21 patients [39] and Shaw et al.'s trial showing superiority over olanzapine in refractory cohorts [40]. Over the past two decades, systematic reviews and a meta-analysis have identified clozapine as probably the most efficacious intervention for refractory EOS [41,42], despite the small pool of trials.

Across three decades, a consistent pattern has emerged: clozapine outperforms comparator antipsychotics in overall symptomatic improvement and, particularly, in reducing negative symptoms. These data underpin its endorsement in international guidelines, typically as a third-line agent for treatment-resistant cases. The American Academy of Child and Adolescent Psychiatry's 2013 Practice Parameter recommends that "a trial of clozapine should be considered for youth with treatment resistant schizophrenia spectrum disorders," noting that it is "the only antipsychotic agent for which there is established superiority over other agents," while the National Institute for Health and Care Excellence advises clozapine after inadequate response to at least two antipsychotics given at therapeutic doses for 6 to 8 weeks each [43,44]. Nevertheless, neither the FDA nor the manufacturer provides guidance on pediatric use; consequently, all such use is off-label. The consistency of guideline endorsement has recently been quantified: in an AGREE II appraisal of 26 national and international guidelines and quality standards for early intervention in psychosis, timely consideration of clozapine in treatment-resistant cases emerged as a core component, endorsed by 14 of 22 documents addressing first-episode psychosis and carrying a strong or mandatory recommendation in eight of them [45]. The same appraisal found the methodological quality of these documents to be only moderate, with variable rigor of development and frequently underdeveloped guidance on applicability and implementation, which helps explain why a recommendation so widely shared translates so unevenly into practice [45]. Indeed, clozapine remains markedly underutilized: a nationwide Danish study found that only 17.6% of EOS cases received clozapine, after an average of three prior antipsychotic trials and a 3.2-year delay [46]. Consistent with this, a survey of child and adolescent psychiatrists in Scotland found that many felt inadequately trained to initiate clozapine, with 35.3% reporting no formal education on prescribing clozapine to pediatric populations [47].

In parallel with adult psychiatry, early pediatric observations suggested benefits beyond psychosis, particularly in severe, treatment-resistant presentations. Observational evidence described clozapine in refractory bipolar disorder, severe aggression associated with neurodevelopmental conditions, and complex affective and behavioral dysregulation (e.g., borderline personality disorder, intermittent explosive disorder, and post-traumatic stress disorder), particularly when standard mood stabilizers and antipsychotics had proved ineffective [34,48–53]. Because RCTs robustly support efficacy only for treatment-resistant EOS, while evidence for other symptom domains remains limited, clozapine is currently used mainly in specialized centers as a last-resort option for youth with diverse refractory psychotic and non-psychotic symptoms [9]. In practice, this off-label use requires solid clinical justification, documented unresponsiveness to prior therapies, guardian consent with patient assent where possible, and a consistently structured clinical monitoring framework [54–57].

These developments mark a gradual conceptual shift: from a molecule tethered to a single, narrowly defined indication to an agent whose therapeutic reach appears to span the dimensions of severe, treatment-resistant psychopathology rather than strictly diagnostic labels. In pediatric practice, where this evolution is anchored in EOS yet increasingly extends to refractory aggression, affective dysregulation, and other complex presentations, it invites a reappraisal of how the clinical value of clozapine is conceptualized, echoing a broader transdiagnostic view now taking shape in adult psychiatry [58]. Building on this historical

development, the next section presents a transdiagnostic rationale for using clozapine in child and adolescent psychiatry.

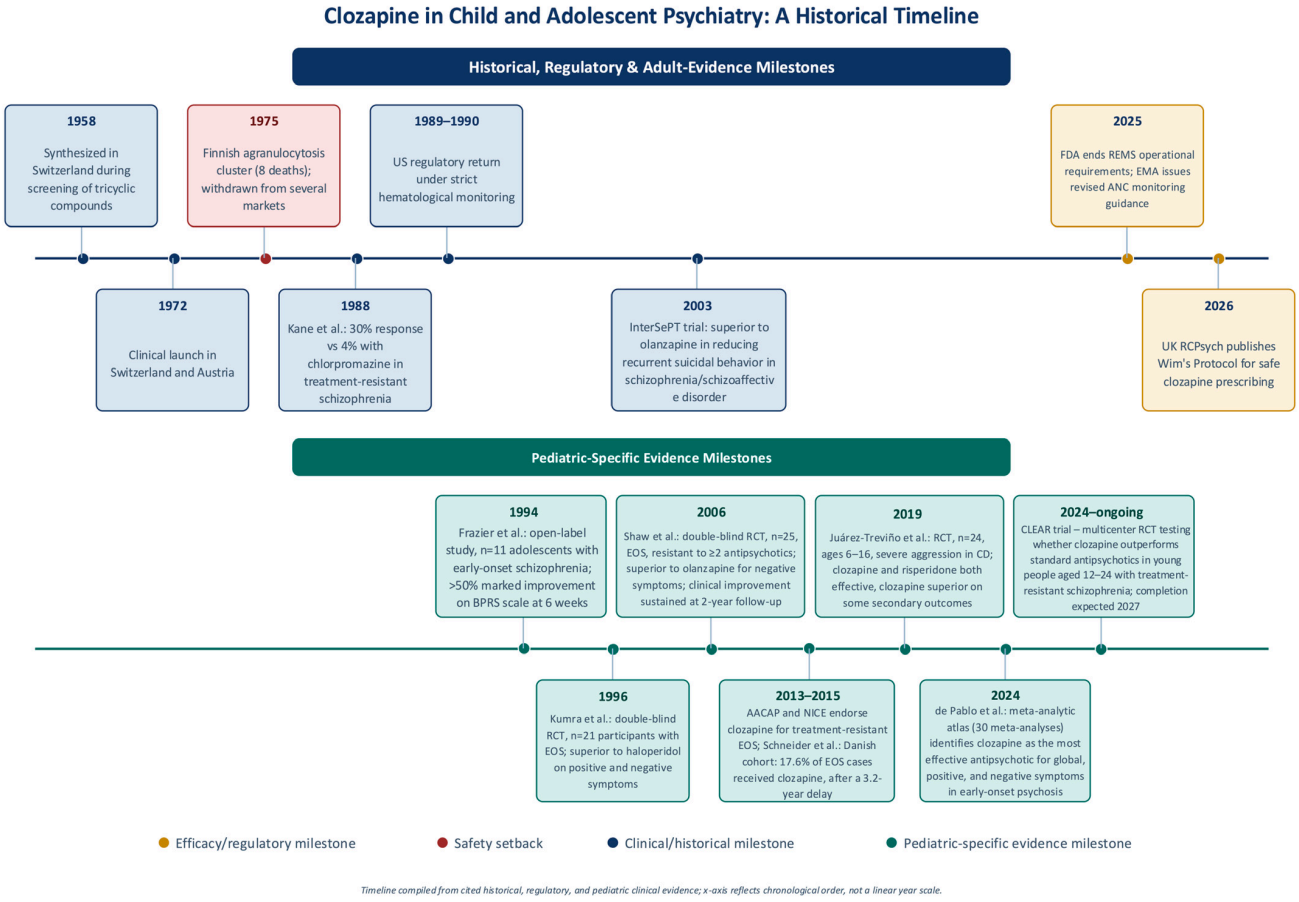



**Figure 1.** Timeline of clozapine use in child and adolescent psychiatry, contrasting historical, regulatory, and adult-evidence milestones (upper track) with pediatric-specific clinical evidence (lower track) along a shared chronological axis. Marker color denotes milestone type: efficacy/regulatory (gold), safety setback (red), general clinical/historical (navy), and pediatric-specific evidence (teal). The horizontal axis reflects chronological order rather than a linear year scale; study details are discussed in the main text. [23,26,38–40,46,59–61].

## 4. A Transdiagnostic Rationale for Clozapine Utility in Child and Adolescent Psychiatry

Transdiagnostic models have emerged as an alternative to the categorical nosology of systems such as the DSM and ICD [62]. Although these categorical frameworks have standardized clinical communication and care, growing evidence indicates that discrete diagnoses poorly capture the comorbidity, symptom covariation, and developmental heterogeneity of child and adolescent mental health [12]. Transdiagnostic approaches focus on shared behavioral, neurobiological, cognitive, and functional dimensions that span multiple disorders and may offer a more integrated basis for assessment, decision-making, and treatment planning [11].

The transdiagnostic perspective rests on three major observations: (1) that distinct disorders can share etiological and neurobiological mechanisms; (2) that clinical features such as functional impairment and illness stage often converge across categories even when mechanisms differ; and (3) that many interventions act across several conditions rather than on disorder-specific targets [63]. High rates of comorbidity in youth, together with

symptom covariation and shared risk factors, reinforce dimensional conceptualizations organized around broad spectra (e.g., internalizing, externalizing, and thought disorder), neurobehavioral traits, and the general psychopathology ("p") factor [12,64–66]. Notably, this dimensional logic has recently been extended to the neurodevelopmental conditions themselves, which have been proposed to be better represented as a neurodevelopmental spectrum within transdiagnostic frameworks than as discrete DSM-5 or ICD-11 categories, given their high co-occurrence, arbitrary diagnostic boundaries, and marked within-disorder heterogeneity [67]. Several frameworks operationalize this shift, including the Research Domain Criteria (RDoC), the Hierarchical Taxonomy of Psychopathology (HiTOP), network models of symptom interaction, and clinical staging [63,68,69] (see Figure 2); each treats psychopathology as multidimensional and dynamic, and implies that interventions may act by modulating shared substrates rather than diagnosis-specific pathways [70].

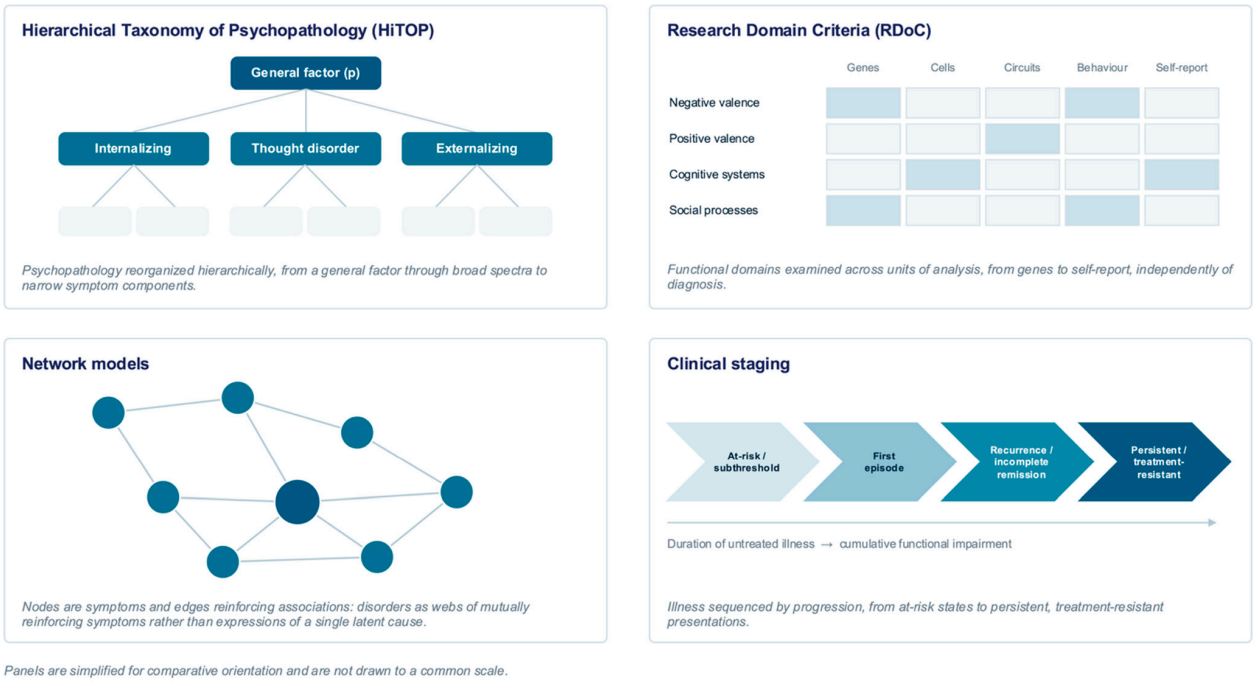



**Figure 2.** Schematic overview of four contemporary transdiagnostic frameworks referenced in this review: HiTOP, which reorganizes psychopathology hierarchically from broad spectra to narrow symptom components; RDoC, which maps functional domains across units of analysis from genes to self-report; network models, which conceptualize disorders as webs of mutually reinforcing symptoms rather than expressions of a single latent cause; and clinical staging, which sequences illness progression from at-risk states to chronic, treatment-resistant stages. Panels are simplified for comparative orientation. Shading is used for visual hierarchy only and does not encode data; the arrow in the clinical staging panel indicates progression over the duration of untreated illness. Panels are simplified for comparative orientation.

A precedent for the transdiagnostic psychopharmacological lens in the field is provided by the selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, used across depressive disorders, anxiety disorders, obsessive-compulsive disorders, and post-traumatic stress disorder [71]. Clozapine can be viewed through a similar lens, with its cross-cutting clinical effects reflecting a pharmacological breadth [1] that distinguishes clozapine from other antipsychotic agents. We hypothesize that, rather than acting through a single, disorder-specific pathway, clozapine engages neural systems involved in salience processing, affect regulation, and impulse control—functions often impaired in severe and complex neuropsychiatric conditions affecting young people (see Figure 3).

Its effects extend beyond dopamine blockade to multiple receptor systems that may help restore function in shared neural substrates. In this context, a prospective neuroimaging study of 22 individuals with TRS showed that response to clozapine correlated with increased corticostriatal functional connectivity between the dorsal caudate and regions of the frontoparietal network. These connectivity changes occurred without significant shifts in striatal dopamine activity, suggesting that clozapine modulates corticostriatal networks through mechanisms beyond dopaminergic pathways [72]. Two early neurochemical observations are often cited in this literature, both from small cross-sectional studies in adults with schizophrenia. Patients treated with clozapine showed higher plasma 5-HIAA levels than patients on typical antipsychotics and healthy controls, consistent with increased serotonin turnover [73], and markedly elevated plasma norepinephrine levels relative to patients on typical antipsychotics [74]. These findings are correlational: neither study tested whether the changes mediate clinical effects, and plasma measures are an uncertain index of central activity, so any link to clozapine's anti-impulsive or anti-aggressive properties remains hypothetical. More recent discussions, following the emergence of the cholinergic antipsychotic compound KarXT, have suggested that the superior antipsychotic efficacy of clozapine may relate to muscarinic activity [6,14]. This activity is not attributable to the parent compound alone: clozapine itself is a muscarinic antagonist or weak partial agonist, whereas its major metabolite, N-desmethylclozapine, is a potent M1 partial agonist and allosteric potentiator of NMDA receptor function [75,76], so that the muscarinic profile of clozapine treatment reflects the combined action of drug and metabolite. Whether this activity relates to improvement in non-psychotic dimensions remains unclear.

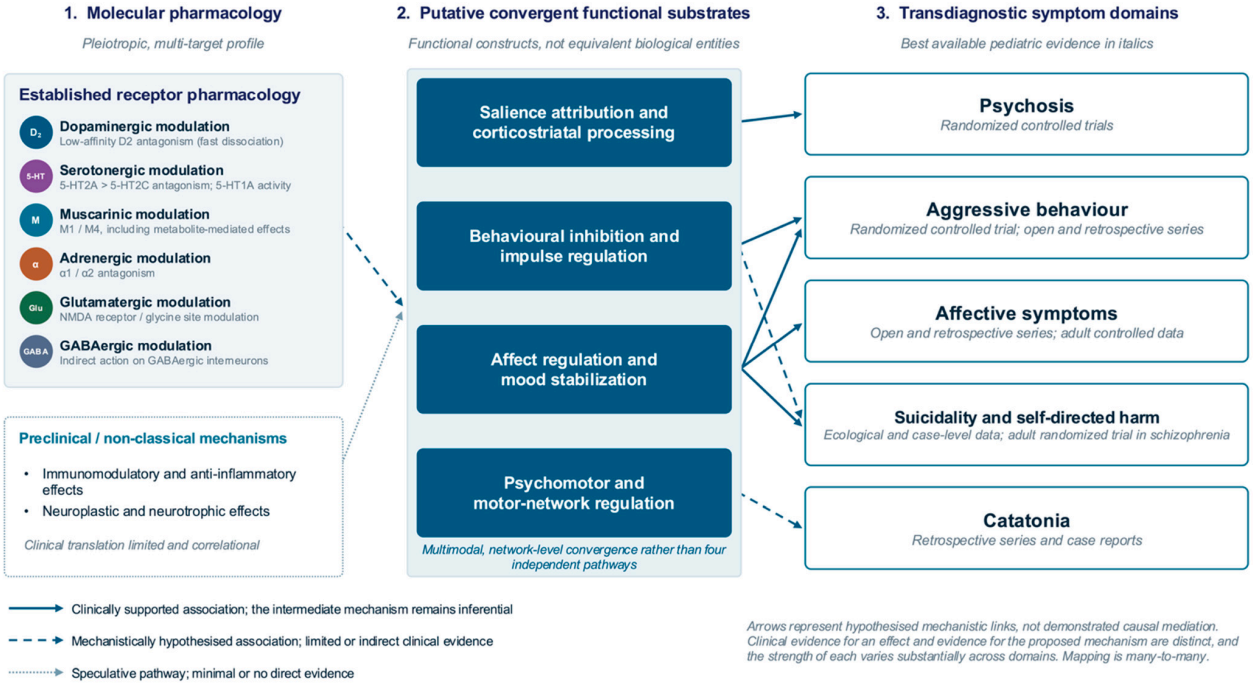



**Figure 3.** Conceptual, hypothesis-generating model of clozapine's multireceptor pharmacology in child and adolescent psychiatry. Molecular pharmacological actions (**left**) are proposed to converge on putative functional substrates (**center**), which may in turn underlie improvement across transdiagnostic symptom domains (**right**). The substrates are functional constructs rather than equivalent biological entities, and the central proposition is convergence at network level rather than four independent causal pathways. Arrow style distinguishes associations for which clozapine's clinical effect is supported but the intermediate mechanism remains inferential (solid), mechanistically hypothesized associations with limited or indirect clinical evidence (dashed), and speculative pathways with minimal or no direct evidence (dotted). Arrows therefore represent hypothesized

mechanistic links, not demonstrated causal mediation; evidence for a clinical effect and evidence for the proposed mechanism are distinct, and the strength of each varies substantially across domains. The best available pediatric evidence is indicated within each domain. Mapping is many-to-many: domains frequently co-occur and may respond concurrently.

The term "transdiagnostic" is used here in three distinct senses, and only the first is supported by the evidence reviewed. In a descriptive sense, clozapine has been used, and has shown benefit, in several diagnoses, but benefit across diagnoses does not show that symptom dimensions or treatment refractoriness predict response independently of diagnosis, because nearly all the studies reviewed were designed and analyzed by diagnosis. In a predictive sense, which is the proposal advanced here, response should track the severity and refractoriness of a symptom dimension rather than the diagnostic label. This remains untested. In a mechanistic sense, shared neurobiological substrates would explain a common response. This is a hypothesis, illustrated in Figure 3, not an established account.

This dimensional reading aligns clozapine with frameworks that prioritize constructs such as psychosis, irritability, impulsivity, and affective dysregulation over rigid categories, a perspective especially suited to child and adolescent psychiatry, where presentations are developmentally dynamic and comorbidity is common. The rationale for situating clozapine within a transdiagnostic framework is therefore mechanistically plausible but still evolving. The following section examines the clinical evidence for this possibility, domain by domain, across pediatric symptom dimensions.

## 5. Domains of Treatment Resistance: Clinical Evidence for Clozapine Across Pediatric Symptom Dimensions

This section organizes the literature by transdiagnostic symptom domain to clarify how clozapine has been used in treatment-resistant cases. The evidence, sparse outside psychosis, is summarized with particular attention to pediatric populations, drawing selectively on studies that also include young adults. This structure seeks to reflect real-world clinical practice, in which decisions are guided by the severity and refractoriness of specific symptom dimensions, alongside diagnosis-based therapeutic choices. The domains differ in certainty. Randomized data exist only for psychosis and, in one small trial, for aggression in conduct disorder; the signal for aggression, suicidality, and refractory affective illness is consistent but largely adult; self-directed harm and catatonia remain exploratory in youth. Because nearly all these studies were designed by diagnosis, the pattern is compatible with, but cannot demonstrate, dimensional rather than categorical prediction of response. These domains frequently overlap, and clozapine may confer benefits across several of them concurrently. Table 1 summarizes the main findings per domain.

Because the framework holds that treatment resistance rather than diagnosis might guide the consideration of clozapine, treatment resistance itself requires definition. Consensus definitions across psychiatry share three components, namely persistent clinically significant symptoms, a sufficient number of adequate treatment trials, and a quantified failure of response, but they vary markedly and are absent for many conditions [77]. Among the domains reviewed here, only psychosis has a validated definition: the Treatment Response and Resistance in Psychosis (TRRIP) consensus requires persistent symptoms and impairment despite at least two adequate antipsychotic trials of at least six weeks each, with confirmed adherence [78], a threshold that pediatric recommendations apply to early-onset psychosis (EOP) [79]. For affective symptoms, consensus criteria exist only in adults (failure of at least two adequate treatments in bipolar depression [80]), whereas pediatric depression trials have used non-response to a single adequate selective serotonin reuptake inhibitor course [81]. Refractory catatonia is defined pragmatically as insufficient response

to an adequate benzodiazepine trial, without standardized thresholds [82]. For aggression and for suicidality and self-directed harm, no operational, validated definition exists at any age, and the studies reviewed here applied heterogeneous, study-specific criteria, ranging from non-response to psychosocial treatment and at least three medications [83] to persistence after two antipsychotic trials [18]. This heterogeneity is a limitation of the evidence and of the framework alike. In the absence of validated criteria, "treatment-resistant" in the sections that follow denotes the definition used by each study.

### *5.1. Psychosis*

Clozapine remains the guideline-recommended standard of care for TRS in both adults and adolescents following the failure of two or more adequate antipsychotic trials [79]. EOP, defined by a first psychotic episode before age 18, is often severe. An umbrella review of 30 meta-analyses on EOP, involving 25,983 participants (mean age 15.1 years), found that 60.1% of EOP individuals had a poor prognosis [60]. Treatment resistance also affects a substantial proportion: 22.8% of first-episode patients develop treatment-resistant psychosis, a figure that may rise to one-third when relapses are taken into account [32]. Despite this, clozapine remains underutilized in EOS, with delays spanning months or years even in specialized settings. As shown by O'Donoghue et al., prior to the implementation of a specialized clozapine clinic, the median time to initiation was 72 weeks, and only 4.6% of young people with first-episode psychosis were started on clozapine [84]. Hence, timely use of clozapine in EOS is widely regarded as important. In the Danish nationwide cohort, most youth who started clozapine had a favorable course, judged by continued prescription redemption and improved occupational outcomes [46], although outcomes were not compared by time to initiation.

The evidence rests on pivotal controlled trials. The first double-blind RCT in children and adolescents found clozapine significantly superior to haloperidol across all measures of psychosis, with marked improvements in both positive and negative symptoms [39]. A subsequent double-blind RCT showed superior outcomes compared with the second-generation antipsychotic olanzapine [40]. A third double-blind trial compared flexibly dosed clozapine with high-dose olanzapine (up to 30 mg/day), with response rates of 66% and 33%, respectively [85]. Contemporary evidence syntheses corroborate these findings and rank clozapine as the drug of choice for treatment-resistant EOS [41,79,86]. In the umbrella review cited above, clozapine was the antipsychotic with the highest efficacy for overall, positive and negative symptoms, and its authors recommend considering it in EOP after resistance to two non-clozapine antipsychotics, the same threshold applied in adults [60]. These gains appear sustained rather than transient: a retrospective analysis of childhood-onset schizophrenia reported strong response with high long-term maintenance rates and suggested that response may be greater in very-early-onset than in adult-onset illness [87]. Similarly, a Korean retrospective study of 26 children and adolescents with refractory early- or very-early-onset schizophrenia found that, after more than a year of clozapine treatment, both hospitalization rate and duration fell significantly relative to the pre-treatment period [88].

Treatment-resistant psychosis extends beyond persistent positive symptoms, and the benefits of clozapine do likewise, with evidence of improvements in negative symptoms, aggression, substance use, suicidality, and global and social functioning [41,89]. A systematic review of substance use disorders other than nicotine among individuals with schizophrenia-spectrum disorders found more favorable outcomes with clozapine than with other antipsychotics [27], a finding relevant to adolescence and young adulthood.

### *5.2. Aggressive Behavior*

Aggression is among the most clinically consequential transdiagnostic domains in youth psychiatry, and the one in which the case for an effect of clozapine independent of diagnosis is best developed. Clinical observations from the 1990s onward suggested that clozapine's anti-aggressive properties are dissociable from its antipsychotic effects [90,91]. Volavka argued that in schizophrenia it addresses violence and substance use simultaneously, reducing craving while exerting independent anti-aggressive effects [92]. A 2012 systematic review of animal and human studies, including RCTs and observational research, supported the specificity of this effect, reporting reductions in aggression proportionally greater than expected from antipsychotic or sedative action alone, with supporting evidence across psychotic and non-psychotic disorders including bipolar disorder, personality disorders, and neurodevelopmental conditions [30]. The scope of this literature was recently mapped by a systematic review of clozapine as a transdiagnostic treatment for aggression, which included 75 reports published up to June 2025: 49 concerned schizophrenia (among them nine RCTs, three registry studies, and fourteen prospective investigations) while the remainder addressed non-psychotic disorders [31]. The anti-aggressive signal is thus reported across, rather than confined to, diagnostic boundaries.

Controlled pediatric evidence outside psychosis comes from conduct disorder. A randomized, double-blind trial compared clozapine with risperidone in 24 children and adolescents aged 6 to 16 years over 16 weeks: both produced comparable reductions in overt aggression, the primary outcome, but clozapine was superior on secondary measures including externalizing behavior, delinquency, and global functioning [59]. This trial followed an open, naturalistic Brazilian study involving seven boys aged 10 to 14 with severe, treatment-resistant conduct disorder. These participants, who had not responded to psychosocial therapy or to at least three medications, were treated for 26 weeks with doses of 100 to 600 mg daily, with good tolerability and significant improvement in conduct symptoms [83].

Within psychotic disorders, the pediatric benefit is evident in outcomes of immediate clinical consequence. In an open-label study of 20 treatment-refractory children and adolescents with schizophrenia aged 8.5 to 18 treated at a state psychiatric center, the frequency of emergency oral medication, emergency injectable medication, and seclusion events during weeks 12 to 24 of clozapine treatment, at a mean dose of 476 ± 119 mg/day, was significantly lower than in the three months preceding initiation, and the improvement was sufficient for patients to be discharged to less restrictive settings [89]. A consecutive chart series of six children and adolescents with childhood-onset schizophrenia or schizoaffective disorder admitted to a long-term care facility similarly recorded fewer violent episodes and seclusion and restraint incidents, reduced homicidal and suicidal ideation, improved social interaction, and functional gains [93].

Aggression in neurodevelopmental conditions, particularly autism spectrum disorder (ASD) and intellectual disability, constitutes a distinct and clinically demanding subgroup [17]. Case reports and series describe reductions in aggression and disruptive behavior following clozapine initiation in children and adolescents with ASD refractory to multiple antipsychotics [94–98], and comparable benefits, including reductions in drug-refractory aggression, in youth with intellectual disability and comorbid psychiatric conditions [99,100]. A retrospective comparison of clozapine-treated autistic and non-autistic children and adolescents found symptom reduction irrespective of ASD status [52]. Larger retrospective series followed: one of consecutively admitted youth with ASD and/or intellectual disability treated for aggression at a tertiary center [53], and a recent chart review of youth and young adults with severe, treatment-refractory irritability and aggression comparing the year before and after initiation [101]. This literature, including a scoping review

by the present authors [17], has been consolidated into a systematic review with expert recommendations, currently the most practice-oriented guidance for this subgroup [57].

The first prospective interventional data in this population have since become available. In a single-arm, open-label trial conducted by the present authors under routine clinical conditions, 31 autistic youth aged 10 to 17 with severe disruptive behaviors persisting after at least two antipsychotic trials received flexibly titrated clozapine maintained for 12 weeks; 28 completed the trial. Caregiver-rated Aberrant Behavior Checklist–Irritability scores fell from 32.0 ± 7.7 to 7.4 ± 5.1 (Cohen's dz −2.5; $p < 0.001$), with 83.9% meeting response criteria and 38.7% achieving remission, alongside improvements in global severity, daily living skills, and caregiver quality of life, and a reduction in polypharmacy. Adverse drug reactions were predominantly mild to moderate, but significant weight gain and triglyceride elevation were observed, and serious events included four seizures and one case of pneumonia [18]. The single-arm design cannot separate the drug effect from the intensified clinical contact that accompanies clozapine initiation, and the primary outcome was rated in an unblinded setting; the magnitude of change should therefore be interpreted cautiously. The study nonetheless provides the first prospectively collected effectiveness and tolerability data in autistic youth treated for this indication, in a literature otherwise composed of retrospective series and case reports.

### *5.3. Affective Symptoms*

Beyond the psychotic dimension, a growing body of evidence suggests that clozapine may benefit children and adolescents with treatment-resistant affective symptoms, although pediatric data remain preliminary and largely uncontrolled.

The strongest evidence for clozapine's efficacy outside schizophrenia comes from severe, treatment-resistant bipolar disorder (TRBD) in adults [102,103]. A systematic review and meta-analysis found that clozapine did not differ from other antipsychotics in acute manic episodes, but was superior to comparator treatments specifically among patients meeting criteria for treatment resistance [104]. This pattern was recently corroborated by a large nationwide transdiagnostic cohort study of participants aged 16 years and older (mean age 41.6 years), in which clozapine was associated with a lower risk of psychiatric hospitalization than other oral antipsychotics not only in schizophrenia and schizoaffective disorder, but also in bipolar disorder, major depressive disorder, and psychotic depression; no such advantage was observed in borderline personality disorder [58]. The advantage therefore appeared to follow severity and refractoriness rather than the diagnostic label, although it was not uniform across all diagnoses.

In youth, the available evidence is considerably weaker but points in the same direction. The most informative pediatric report on potential mood-stabilizing properties remains a prospective open series of 10 adolescent inpatients aged 12 to 17 years with severe manic or mixed episodes refractory to mood stabilizers and antipsychotics: all were rated as responders on the Clinical Global Impression–Improvement (CGI-I) scale by discharge, 15 to 28 days after initiation, with concurrent reductions on the Young Mania Rating Scale and the Brief Psychiatric Rating Scale [105]. Case series before and since describe improvement in most children and adolescents treated after failure of other antipsychotics, whether for bipolar disorder or EOS, generally at modest doses and without added polypharmacy [34,50]; a single case report describes a 13-year-old with TRBD and comorbid obsessive–compulsive disorder who improved on clozapine combined with lithium and clomipramine after failing standard treatment [48]. The largest pediatric dataset to date is a multicenter retrospective study of 82 youth hospitalized for acute psychiatric illness; a quarter (25.6%) carried a primary diagnosis of bipolar disorder. Overall, 95% of the full cohort were discharged on clozapine, with more than half showing moderate or significant improvement [51].

Beyond mood symptoms proper, clozapine may act on the high-risk behaviors that cluster around severe affective illness. Individual case reports describe marked reductions in self-injurious behavior alongside improvement in mood symptoms following clozapine initiation in adolescents with treatment-resistant depression and recurrent suicide attempts, with explicit weighing of the risk-benefit trade-off in young suicidal patients [106,107]. This remains case-level evidence and should be read as hypothesis-generating.

### *5.4. Suicidality and Self-Directed Harm*

Non-suicidal self-injury (NSSI) and suicidal behavior are distinct clinical phenomena. NSSI occurs without an intention to die and often serves emotional-regulation or interpersonal functions; it also follows a developmental course that differs from that of suicidal behavior [108,109]. At the same time, the two share considerable risk overlap. NSSI is among the strongest predictors of later suicide attempts, the two behaviors frequently co-occur in the same individuals at rates exceeding chance, and both are associated with impulsivity, affective instability, and behavioral dyscontrol rather than with any single diagnostic category [110,111]. Both are transdiagnostic, appearing across depressive, bipolar, psychotic, post-traumatic, eating, and personality disorders [112]. The clozapine literature, however, has rarely distinguished between them, often combining self-directed harm behaviors into a single endpoint.

The evidence is strongest, and of the highest design quality, in schizophrenia-spectrum disorders. The International Suicide Prevention Trial (InterSePT), an open-label randomized trial with masked outcome raters, assigned 980 patients aged 18–65 years with schizophrenia or schizoaffective disorder at high risk of suicide to clozapine or olanzapine for a two-year study [26]. Compared with olanzapine, clozapine reduced the hazard of the prespecified type 1 composite endpoint (i.e., significant suicide attempts, including fatal attempts, or hospitalization to prevent suicide) by approximately 24% (HR 0.76, 95% CI 0.58–0.97, $p = 0.03$). Suicide deaths were infrequent and did not differ significantly between groups. Treatment resistance was not an eligibility requirement, and only 26.8% of participants were treatment-refractory, indicating that the evidence was obtained in a population not restricted to treatment-resistant illness [26]. Observational studies converge on superiority over other antipsychotics for suicidal behavior and suicide-related mortality, apparently independent of differences in monitoring intensity or baseline risk [113,114]. On this basis, clozapine holds the only FDA regulatory indication specifically for reducing recurrent suicidal behavior in schizophrenia and schizoaffective disorder [115], and it remains one of the few psychotropics with randomized trial evidence demonstrating a direct anti-suicidal effect. Conversely, discontinuation of clozapine has been associated with increased suicidality [7]. A disproportionality analysis of the World Health Organization (WHO) global pharmacovigilance database (VigiBase) examined four outcomes on the suicidality spectrum: suicidal ideation, suicide attempt, intentional overdose, and completed suicide [116]. Because the information component (IC) measures reporting disproportionality relative to all other drugs in the database, every antipsychotic analyzed showed positive ICs for these outcomes, an expected consequence of the high baseline risk of the populations treated. The informative comparison is therefore between antipsychotics: clozapine's IC was significantly lower than that of all comparator antipsychotics for all four outcomes. For completed suicide, for example, clozapine's IC was 1.133 (IC025 = 1.026, IC975 = 1.235), whereas comparator values ranged from 2.160 for risperidone to 4.648 for quetiapine [116].

Evidence outside schizophrenia-spectrum disorders is of lower certainty but still warrants attention. A systematic review of suicide prevention with clozapine suggests a possible role in severe, treatment-resistant suicidality and NSSI in bipolar disorder and borderline personality disorder (BPD), while noting that the supporting evidence is limited in both

level and quality [7]. Most of it concerns BPD, the diagnostic context in which recurrent self-harm is most characteristic. A systematic review of clozapine for severe treatment-resistant BPD identified a single RCT, with the remaining literature consisting of non-controlled trials and case reports; across these low-certainty data, the reported signals suggest benefits for patients with BPD who are frequently hospitalized and remain at high suicide risk despite psychotherapy and other pharmacological trials [29]. Adolescent-specific data are restricted to isolated descriptions of severe, treatment-refractory borderline pathology, with no controlled pediatric study available [49]. Register-based evidence contrasts with this picture: in the largest real-world comparison to date, clozapine was associated with lower rates of psychiatric hospitalization relative to other antipsychotics across psychotic and affective diagnoses but conferred no comparable advantage in personality disorders [58].

Pediatric evidence is thinner still and derives from three convergent but individually weak sources. A structured review of pharmacological treatments for suicidality in individuals under 18 identified only a small number of investigations involving clozapine, in which suicidality and self-injury were rarely primary outcomes because the interventions were designed around categorical diagnoses rather than around the behavior [117]. Case reports describe marked and sustained reductions in self-harm after multiple treatment failures, including recurrent NSSI controlled with low-dose clozapine monotherapy [118] and self-injury in adolescents with treatment-resistant depression and recurrent suicide attempts [106,107]. Population-level data offer independent, if indirect, support: regional use of clozapine, electroconvulsive therapy (ECT), and lithium has been linked to lower excess suicide mortality among male adolescents in 21 Swedish regions [119], and a French analysis of regional prescriptions and pediatric self-injury and suicide mortality between 2014 and 2019 reported findings consistent with an anti-suicidal effect, with a less clear signal for lithium, while documenting marked inequities in access within a health system that offers free services [120]. Both designs are ecological and cannot support causal inference, nor can they distinguish an effect on suicide from an effect on the severity of the illnesses in which suicide occurs. Their convergence with the adult literature is nonetheless notable.

This domain carries a paradox absent elsewhere in this review: the agent proposed to reduce suicidal behavior is itself lethal in intentional overdose, with a case fatality of 14.3% reported in pharmacovigilance data [116].

### *5.5. Catatonia*

Catatonia is a neuropsychiatric syndrome of altered movement, speech, and behavior. Historically tied to schizophrenia, it is now recognized as transdiagnostic, occurring across bipolar disorder, major depressive disorder, neurodevelopmental conditions, and a range of medical and neurological illnesses [121]. Additionally, DSM-5-TR codes catatonia as a specifier applicable across diagnoses, and ICD-11 recognizes it as an independent entity [122,123]. Benzodiazepines and ECT remain first-line [82], yet response is incomplete: in a systematic review and meta-analysis of benzodiazepine treatment, the overall response rate was 77%, but remission was achieved in 55% [124], and patients with underlying psychotic disorders are over-represented among non-responders [82].

Both first- and second-generation antipsychotic agents may exacerbate catatonic signs or increase the risk of neuroleptic malignant syndrome, although the risk appears to be greater with first-generation antipsychotics [125]. Clozapine is among the few antipsychotics reported to benefit this population [126], and this contrast underlies the suggestion that it possesses genuinely anti-catatonic properties rather than merely suppressing symptoms. Proposed mechanisms include indirect action on receptors located on GABAergic interneurons, distinct from the positive allosteric modulation of GABA-A, together with

adaptations in dopaminergic and cholinergic systems [127]; these remain hypotheses, and the mechanisms of established anti-catatonic treatments are themselves nonspecific [128].

Evidence specific to youth is beginning to emerge from neurodevelopmental populations, where catatonia is both under-recognized and clinically consequential, and where diagnosis is complicated by overlap with the core features of autism [129]. The benzodiazepine-refractory subgroup is substantial: in a 12-year retrospective series of 22 autistic youth with catatonia, 21 initially failed benzodiazepines at doses ranging from 1 to 27 mg daily and all proceeded to ECT, with treatment-resistant catatonic self-injury among the symptoms relieved [130]. Within this context, a retrospective chart review of 12 individuals with autism spectrum disorder and catatonia reported high rates of response and adherence to clozapine, supporting its use when lorazepam is ineffective or only partially effective [131], complementing earlier case descriptions in the same population [132]. A more recent series extends these observations across neurodevelopmental conditions: among 20 youth with catatonia and co-occurring psychotic symptoms, treated at a single tertiary center between 2017 and 2025, improvement followed benzodiazepine treatment in 75% and the first antipsychotic trial in 60%, with worsening documented in 10%. ECT was used in 60% and clozapine in 35%. Because interventions overlapped and no control group was available, these outcomes characterize contemporary prescribing patterns rather than the effect of any single agent [133].

Chronic and periodic catatonia poses a distinct management challenge, often requiring treatment over months or years. In these cases, clozapine at doses below the typical psychosis range (<150 mg/day) is listed alongside maintenance ECT and psychotherapeutic strategies, particularly when catatonia is associated with psychotic features [134].

Clozapine withdrawal catatonia offers an independent line of evidence. In a review of 55 published cases of withdrawal catatonia, 20 followed clozapine discontinuation and 24 followed benzodiazepine discontinuation. No other antipsychotic was associated with onset of a catatonic episode within two weeks of withdrawal [127]. This effect is difficult to attribute to the confounders that limit uncontrolled case series.

**Table 1.** Transdiagnostic symptom domains: summary of clinical evidence for potential clozapine utility.

| Symptom Domain | Predominant Evidence Base | Key Clinical Findings |
| --- | --- | --- |
| Psychosis | RCTs and systematic reviews/meta-analysis (strongest evidence base) | – First double-blind pediatric RCT: superior to haloperidol across positive and negative symptoms [39]<br>– Superior to olanzapine, including high-dose regimens [40,85]<br>– Ranked the most efficacious agent for treatment-resistant early-onset schizophrenia in evidence syntheses [41,60]<br>– Improvement spans positive and negative symptoms and global/social functioning [41,85,89] |
| Affective symptoms | Adult systematic review/meta-analysis and register cohort in treatment-resistant bipolar disorder; pediatric evidence limited to case series and reports | – Adults: superior to comparators specifically in treatment-resistant bipolar disorder [104]; register cohort showed lower psychiatric hospitalization in bipolar, depressive, and psychotic-depression diagnoses [58]<br>– Prospective series of 10 adolescents with refractory mania/mixed episodes: all rated responders (CGI-I) by discharge [105]<br>– Multicenter retrospective study, inpatient setting, $n = 82$ (25.6% bipolar disorder): 95% discharged on clozapine, over half moderately or markedly improved [51]<br>– Case reports of benefit in treatment-resistant depression with chronic suicidality [106,107] |

**Table 1.** *Cont*.

| Symptom Domain | Predominant Evidence Base | Key Clinical Findings |
| --- | --- | --- |
| Aggression | Systematic review (animal + human, incl. RCTs); one pediatric RCT (conduct disorder) and a prospective open-label trial (autistic youth); observational series | – Anti-aggressive effect proportionally greater than expected from antipsychotic/sedative action alone ("specific" effect) [30,31]<br>– Conduct disorder RCT ($n = 24$) vs. risperidone: comparable on aggression but superior on externalizing behavior and global functioning [59]<br>– Prospective open-label trial in autistic youth ($n = 31$): large reductions in treatment-resistant disruptive behaviors, with 83.9% response rate over a flexible-titration period followed by 12 weeks on a stable dose of clozapine (present authors) [18] |
| Suicidality and self-directed harm | Strongest evidence from an RCT in schizophrenia-spectrum disorders (InterSePT); pharmacovigilance and population-level data; in youth, case reports only, with self-directed harm rarely a primary outcome | – InterSePT (ages 18–65): HR 0.76 for suicide attempts or hospitalization to prevent suicide vs. olanzapine (~24% relative reduction); no difference in suicide deaths [26]<br>– Clozapine is the only drug with an FDA indication for reducing the risk of recurrent suicidal behavior in schizophrenia-spectrum disorders [115]<br>– Population-based data link regional clozapine use to lower excess suicide rates in male adolescents [119]<br>– Marked, sustained reductions in suicidal ideation and self-harm in adolescents after multiple prior treatment failures [106,107]; recurrent NSSI controlled with low-dose clozapine in isolated reports [118]<br>– Methodological and ethical constraints limit RCTs in high-risk youth [117] |
| Catatonia | Retrospective series and case reports in youth with neurodevelopmental and/or psychotic disorders; review of withdrawal-catatonia cases | – Retrospective chart review in 12 autistic youth: high response and adherence when benzodiazepines were ineffective [131]<br>– Potentially effective alternative for chronic, recurrent forms of catatonia [134]<br>– Clozapine withdrawal catatonia responds poorly to benzodiazepines but resolves reliably with clozapine reinstitution [127]<br>– Pediatric-specific data remain limited [132,133] |

Abbreviations: CGI-I, Clinical Global Impression–Improvement; InterSePT, International Suicide Prevention Trial; NSSI, non-suicidal self-injury; RCT, randomized controlled trial.

## 6. Clozapine's Real-World Signals Across Diagnostic Categories in Youth: Further Evidence for a Transdiagnostic Conceptual Framework?

The domains reviewed above were mostly defined by symptomatic endpoints. A complementary question is whether those gains reach the outcomes that shape a severely ill young person's trajectory: admission, length of stay, seclusion and restraint, emergency contact, and the number of concurrent medications needed to maintain stability. Because such endpoints are generated in routine care, they form a line of evidence partly independent of the small, uncontrolled samples described above. A 2026 retrospective study from Türkiye comparing adolescents with ASD and schizophrenia-spectrum disorders reported effectiveness and tolerability that compared favorably with the polypharmacy regimens the patients had received before initiation [135], although a retrospective design cannot attribute this benefit to clozapine rather than to the concentrated clinical attention accompanying its introduction.

The same pattern recurs across otherwise dissimilar pediatric presentations, though the supporting designs differ in strength. In EOS, a systematic review and meta-analysis reported reductions in hospital admissions and length of stay together with gains in global functioning [41]; in ASD with severe irritability, a retrospective case series recorded a decline in emergency department visits [98], and the prospective open-label trial described above found improvement on the Vineland-3 Daily Living Skills domain [18]; and in conduct disorder, in the randomized trial discussed above, clozapine separated most clearly from risperidone not on aggression scores, its primary outcome, but on global functioning and other secondary measures [59]. What these heterogeneous cohorts share is not a diagnosis but a service-use profile before initiation: repeated admission, coercive measures, and escalating polypharmacy. The adult literature is larger and methodologically stronger. In a 2025 nationwide, within-individual cohort study of Finnish and Swedish registries (over 500,000 individuals aged 16 years or older, 19,910 of them clozapine users), clozapine was associated with lower rates of psychiatric hospitalization relative to other oral antipsychotics in every diagnostic category examined except BPD, outperformed mood stabilizers in bipolar disorder, and did so without any increase in all-cause hospitalization or mortality and with lower discontinuation than olanzapine [58].

That exception is instructive, because a different design applied to the same diagnosis yields a different answer. In a two-year mirror-image study of Danish register data, patients with BPD were compared with themselves before and after clozapine initiation, and the treatment period was associated with a reduction in psychiatric hospitalization [136]. The divergence is a property of the comparison: a within-individual before-and-after design asks whether a patient fares better after starting clozapine than while deteriorating toward it, whereas a between-drug design asks whether clozapine fares better than the alternatives. Mirror-image estimates are also exposed to regression to the mean and to the intensified clinical contact that clozapine imposes, the confounder already noted for the single-arm, open-label pediatric trial in autistic youth [18].

These signals must be weighed against the quality of the evidence behind them. The pediatric base consists of case series, open-label cohorts, and retrospective chart reviews without control groups; a PRISMA-compliant systematic review of clozapine use in children for non-psychosis indications reached the same conclusion [10], as did earlier and more recent pediatric reviews and retrospective series [9,137]. The service-use endpoints most often reported, namely admission, restraint, and emergency contact, are also those most sensitive to the intensified monitoring that clozapine initiation imposes. Compounding this, clozapine still lacks FDA approval and manufacturer guidance for pediatric use, and children may be particularly vulnerable to adverse effects, with developmental pharmacokinetic factors potentially contributing to this risk [138,139].

## 7. Clinical Management and Safety in Youth

Realizing this potential depends as much on how clozapine is used as on whether it is offered to most severely ill youth. Many of the barriers identified above appear to be logistical and procedural rather than related to uncertainty about efficacy [5,47], and a dimensional indication widens the population in whom an off-label decision must be made. A proposal to extend clozapine beyond its licensed indication therefore carries an obligation to state what safe extension requires. What follows sets out the requirements that demand particular caution in children and adolescents. It does not substitute for general prescribing guidance [56], nor for the expert recommendations proposed for specific neurodevelopmental populations [57].

Precision dosing is the first requirement. Children and adolescents are especially vulnerable to metabolic and neurological adverse effects, and ancestry-related differences in CYP1A2 activity, compounded by tobacco-smoke exposure and systemic inflammation, generate variability that current pharmacogenomic markers only partly explain [140,141]. Therapeutic drug monitoring should therefore be strongly considered whenever available, with particular vigilance during inflammatory states, which can suppress CYP1A2 and precipitate toxic accumulation [142,143]. The pediatric basis for such monitoring is thin: a systematic review of concentration-to-dose ratios in children and adolescents screened 37 articles but found only seven reporting trough steady-state concentrations [16], while ancestry-informed pharmacokinetic and pharmacogenomic analyses have drawn on predominantly adult datasets [140]. Where monitoring is available, dose-concentration-response relationships have been described in pediatric practice [139,144], providing an empirical starting point for target ranges. The practical consequence is that in this age group the milligram dose is a poor proxy for exposure, so that a measured plasma concentration, where obtainable, should guide adjustment in preference to dose alone.

Three practical parameters follow. First, the therapeutic reference range established in adults is 350 to 600 ng/mL, with a laboratory alert level of 1000 ng/mL [145]; no pediatric range has been validated, the pediatric monitoring data available describe concentration–dose relationships rather than response thresholds [16,139,144], and young people may respond at lower concentrations than those expected in adults [146], so these targets are extrapolated and should be interpreted alongside clinical response and tolerability. Second, titration should be slower than adult schedules. Recent guidance for prescribers treating young people advises initiation at 12.5 mg/day, or 6.25 mg/day in community settings, with smaller increments and a longer titration period than in adults, while acknowledging that no standardized pediatric schedule exists and that adult schedules are adapted in practice [146]. Third, gastrointestinal hypomotility warrants protocolized prevention rather than reactive treatment: bowel function should be assessed at every visit, an osmotic laxative such as macrogol started prophylactically at initiation, bulk-forming laxatives and concomitant anticholinergic drugs avoided, and treatment escalated according to a predefined algorithm, as in the Porirua Protocol developed for adults [147]; a similar prophylactic approach was applied in the pediatric trial described above [18].

Safety surveillance likewise needs rebalancing. Hematological monitoring has understandably dominated practice since the 1975 Finnish events, and absolute neutrophil count monitoring remains non-negotiable; yet the largest pediatric-specific pharmacovigilance analysis available indicates that mortality in this age group is not concentrated in the hematological domain around which monitoring schedules are built. Among reports concerning patients under 18 years submitted to the WHO's VigiBase from clozapine's introduction to June 2022, decreased white blood cell count was by far the most frequently reported adverse drug reaction, accounting for 934 of the cases analyzed, yet only one of these had a fatal outcome (0.1%, 1/934) [148]. Of 27 non-duplicated fatal outcomes, the leading causes were suicide (seven), clozapine-induced gastrointestinal hypomotility (three), and neuroleptic malignant syndrome (two), while agranulocytosis, aspiration, myocarditis, cardiomyopathy, and ventricular arrhythmia each accounted for one; relative lethality was also lower in this age group than across all ages (1.5% versus 11.7%). Spontaneous-reporting data cannot yield incidence rates and are subject to differential reporting, so these proportions describe the distribution of reported deaths rather than absolute risk. They nonetheless point in the same direction as the pattern assembled in this review, and the authors draw the corresponding practical conclusion: that child and adolescent psychiatrists should shift attention from severe neutropenia toward pneumonia, respiratory aspiration, and clozapine-induced gastrointestinal hypomotility, which can progress to life-threatening presentations [148,149].

To these the literature adds neurological and rapid-onset cardiovascular and metabolic complications [150–153]. The present authors' trial illustrates the neurological risk. Among 31 autistic youth, four (12.9%) had seizures, all in participants with pre-existing epilepsy, a comorbidity present in 11 of the 31 (35.5%). These events occurred despite conservative titration (25-mg increments every 2 to 4 days from a starting dose of 12.5 to 25 mg/day) and at a mean final dose of 289 mg/day. The published report does not relate individual seizures to dose or titration stage, and plasma concentrations were not systematically measured [18]. In youth with comorbid epilepsy, therefore, seizure risk is present even at modest doses, which argues for antiepileptic review before initiation, attention to concomitant drugs that lower the seizure threshold, and a low threshold for plasma-level measurement. Prescribing clozapine to youth therefore requires clinicians who maintain a high index of suspicion across this broader range of adverse reactions, know how each presents in this age group, and manage them proactively rather than reactively [18].

This rebalancing is already underway, but so far only in adult practice. Wim's Protocol, issued by the Royal College of Psychiatrists (UK) in 2026 after an inquest into a death from undetected clozapine-associated myocarditis, extends structured surveillance well beyond hematology to serial cardiac markers and electrocardiogram during titration, scheduled cardiometabolic checkpoints, protocolized management of gastrointestinal hypomotility, plasma level monitoring, and ten red-flag symptoms framed for carers and non-specialist clinicians as well as prescribers [154]. The domains it prioritizes are precisely those the pediatric pharmacovigilance data identify as most lethal in this age group. Yet the protocol explicitly excludes children and young people, deferring them to future editions. In Europe, a joint expert statement from the European Clozapine Task Force argues that the incidence of clozapine-induced agranulocytosis becomes very low after the first year and that current blood-monitoring rules should be revised to improve access [155], and revised hematological monitoring recommendations have since been proposed [25]. Whether such relaxation should extend to children and adolescents—in whom benign hematological variation is more common but early adverse events are less reliably reported—remains unaddressed. A further implication follows from the same pharmacovigilance data: because suicide was the single most frequent cause of death among the pediatric fatal outcomes [148], and because clozapine is lethal in overdose, prescribing to a young person at suicide risk requires explicit safeguards over supply, quantities dispensed, and medication storage. Until a pediatric-specific framework exists, clinicians are left adapting adult protocols with caution rather than certainty. Whatever surveillance schedule is adopted, clozapine carries no pediatric labeling, so every prescription remains an off-label decision requiring documentation, caregiver consent, and, where developmentally appropriate, patient assent [54].

The regulatory frameworks within which these recommendations apply differ across jurisdictions. To our knowledge, clozapine is not approved for children in any country, and in the United Kingdom, its license starts at 16 years [146]. Pediatric use is thus off-label everywhere, with local safeguards in place. Hematological monitoring also varies: the UK requires mandatory registration with brand-specific monitoring services and threshold-based actions; the US discontinued mandatory REMS participation in 2025 but still mandates neutrophil monitoring in the labeling; and the European Medicines Agency recommends monitoring by absolute neutrophil count alone, every 12 weeks after the first year and annually after the second [24,25,146]. These regimes were not designed for minors, so until a pediatric protocol is established, clinicians should adhere to the locally mandated schedule, bearing in mind the pediatric-specific cautions regarding hematological variation noted above.

## 8. Discussion

Taken together, the evidence reviewed here portrays clozapine as an unusual case in child and adolescent psychopharmacology: an agent whose efficacy in treatment-resistant EOP is well established, yet whose clinical footprint remains disproportionately small relative to the population that might benefit. Across the psychopathological domains examined, the findings are compatible with a broadly similar signature of benefit once treatment resistance is genuine and severe, despite the differing diagnostic labels attached to these presentations, but this pattern should be regarded as a hypothesis to be tested. On this basis we propose that clozapine be reconceptualized less as a diagnosis-specific antipsychotic than as a pharmacological strategy targeting core dimensions of refractoriness. That a diagnostic label may function as the setting rather than the target of treatment is suggested by our earlier scoping review of clozapine in severe psychiatric symptoms co-occurring with ASD: across 46 studies and 122 individuals, the reported benefit distributed itself across four refractory symptom dimensions (i.e., disruptive behavior, psychotic symptoms, catatonia, and mood symptoms) rather than one diagnosis, though the underlying evidence, largely observational, warrants cautious interpretation [17].

This reframing should be stated for what it is. It is inferred backward from an observed pattern: clozapine appears useful across several symptom domains, and plausible shared mechanisms are proposed after the fact to account for it. It has not been tested forward. No pediatric study has prospectively shown that patients with a stronger signature of the proposed convergent substrates respond more broadly across domains, nor has the model been examined for discriminant validity against other broad-spectrum agents. Because trial design in child psychiatry remains almost entirely diagnosis-based, a dimensional conceptualization sits awkwardly within the prevailing architecture, much as RDoC and HiTOP do within broader nosology [63]. The model is therefore best treated as an organizing heuristic where clozapine is already under consideration on domain-specific grounds, not as a framework that would justify expanding its use preemptively. A framework of this kind also requires boundary conditions, that is, domains in which it predicts no advantage. The evidence reviewed suggests two: the core social-communication impairment of autism, which did not change in the prospective trial even as disruptive behavior improved [18], and obsessive-compulsive symptoms, which clozapine is known to induce or exacerbate [156]. The personality-disorder findings offer a sharper test. If benefit tracks the severity and refractoriness of symptom dimensions rather than the diagnostic label, clozapine's advantage over other antipsychotics within BPD should be concentrated in the subgroup with severe, treatment-resistant self-directed harm or aggression and absent elsewhere in the diagnosis. A diagnosis-level null, as in the register study [58], is compatible with this prediction. A null confined to that high-severity subgroup would falsify it, whereas a uniform advantage across severity strata would favor a categorical account. The same stratified comparison against other broad-spectrum antipsychotics would supply the test of discriminant validity the framework presently lacks.

Mechanistic plausibility does not imply uniform strength of evidence. For treatment-resistant early-onset schizophrenia-spectrum disorders the case rests on randomized controlled data spanning three decades, and it is here that guideline recommendations speak with greatest confidence [43,44]. Beyond that core indication the evidence thins abruptly, resting on case series, retrospective cohorts, and extrapolation from adult studies. The register-based study by Luykx et al. presented above is the most robust of these, and it sharpens the picture rather than settling it [58]. The benefit it documents extends across psychotic and affective categories but stops at personality disorder. That the mirror-image estimate in the same diagnosis [136] points the other way shows how much a real-world result depends on the comparison chosen. Because that evidence is exclusively adult, the

strongest support for a transdiagnostic reading now comes from a design that no pediatric study approaches. The pediatric shortfall therefore concerns study design as well as sample size, and further case series will not close it.

Converging evidence, from the InterSePT trial through pharmacovigilance and population-level data [26,116,119], raises the possibility of a reduction in suicidal behavior extending beyond schizophrenia-spectrum disorders, which matters given that suicide is a leading cause of adolescent death worldwide. Adolescent-specific pharmacovigilance data now speak to this directly: in VigiBase, across more than 1000 reports of suicidal behavior among 12–17-year-olds treated with antipsychotics, clozapine showed significantly lower reporting disproportionality (IC) than comparator antipsychotics for suicidal ideation, suicide attempt, completed suicide, and overdose, with a profile closely mirroring that of the all-age sample [157]. As spontaneous reports uncontrolled for diagnosis, illness severity, and reporting bias and resting on very small numbers of completed suicides, these data cannot establish causation; what they do is align the pediatric signal with the adult literature and suggest that the mortality most feared in youth is not the mortality most often observed. A similar argument has recently been made at the population level in adults. Agranulocytosis accounts for only 3% of fatal clozapine outcomes worldwide, and in a Veterans Affairs cohort of 6488 patients followed for up to 23 years, mortality from severe neutropenia was 0.03%. Set against suicide-risk reductions of up to 80% reported in registry data for patients who take clozapine consistently [158], the imbalance is striking. A projection in a recent commentary on adults with schizophrenia illustrates the asymmetry [158]: assuming a world population of 8 billion, a 1% prevalence of schizophrenia, a 5% lifetime risk of suicide, lifelong consistent clozapine use by 10% of those affected (8 million people), and prevention of 80% of their suicide deaths, some 320,000 suicides would be averted, whereas applying the 0.03% mortality of the Veterans Affairs cohort to the same 8 million yields approximately 2400 deaths from agranulocytosis. Each input is an upper-bound or extrapolated estimate, the treated population is not restricted to treatment-resistant cases, and none of the figures has been estimated in youth. Even under far more conservative assumptions, however, the balance would remain strongly favorable, which raises the possibility that current risk perceptions reflect a mismatch between the mortality clinicians fear and the mortality patients face. Mortality is the gravest of these stakes, but not the only one. A developmental argument can also be made, although it remains a hypothesis in youth. Prolonged exposure to uncontrolled psychosis, severe aggression, or affective dysregulation during developmentally sensitive periods may add to cumulative functional impairment, and treatment resistance may be less a fixed state than a process in which repeated therapeutic failures push a young patient toward chronicity. Clinical staging models, including those developed for young people, link a longer duration of untreated illness to worse outcomes [159–161], and in adults with treatment-resistant schizophrenia longer delays to clozapine initiation have been associated with poorer symptomatic outcomes [162]. In youth, however, the data document delay and underuse rather than their consequences: to our knowledge, no pediatric study has compared outcomes by time to clozapine initiation, and the only prospective pediatric interventional data in autistic youth showed marked behavioral improvement over about 12 weeks on a stable dose of clozapine, with no change in overall adaptive functioning [18]. Whether earlier clozapine use can stabilize a developmental trajectory therefore remains untested. Underuse itself is well documented. A survey of 517 child and adolescent psychiatrists in Türkiye captures the gap plainly: 92.3% agreed that clozapine is more effective than the alternatives, yet only 30% had prescribed it in the past year and fewer than a third had ever been trained in its use [163]. Their concerns centered on adherence and blood monitoring rather than efficacy, and the hesitation was greatest among residents and among clinicians without

access to an inpatient service, who were roughly half as likely to have seen clozapine used in training [163]. These findings suggest that limited training and preparedness, rather than doubts about efficacy alone, may represent important barriers to clozapine use. Whether such delays are clinically neutral in youth is an open question, which prospective cohorts comparing outcomes by time to initiation, in young people of comparable refractoriness, could address.

None of this is stronger than the evidence it rests on, and several limitations of this review should be made explicit. As a narrative synthesis organized around a transdiagnostic thesis, it followed no registered protocol and applied no systematic screening procedures or formal risk-of-bias appraisal, leaving it open to selective citation and to a preference for positive reports. The search proceeded in two stages, a structured search up to March 2026 followed by unstructured surveillance of subsequently published work. The second stage may favor recent and positive findings. Two studies conducted by the present authors [17,18] carry considerable weight in the aggression domain and were included under the same criteria as the rest of the literature, but the potential for confirmation bias cannot be excluded. The restriction to English-language records is a further constraint, since part of the early evidence exists only in German and was accessible here through secondary appraisal [19]. Treatment resistance, the construct on which the framework rests, has a validated operational definition only for psychosis. In the remaining domains it was defined heterogeneously by the individual studies, which limits comparability across the evidence and constrains how the framework can be applied and tested. Finally, the evidence itself is thin: pediatric samples are small and heterogeneously dosed, standardized drug monitoring is largely absent, and much of the data come from a few specialized centers. Pharmacokinetic, pharmacogenetic, and long-term outcome data specific to children remain scant, and what does exist to guide clinical practice is often extrapolated from adults [16,146].

## 9. Conclusions

The shift proposed here concerns the question asked rather than the drug used: not which diagnosis justifies clozapine, but which severe and refractory symptoms might respond to it. Since the evidence is strong only in treatment-resistant EOS and largely observational elsewhere, this remains a working heuristic grounded in pharmacology, not a validated framework. Tested prospectively and combined with efforts to shorten the long delays that precede a clozapine trial, it could still bring an underused drug to more young people whose presentations look intractable. Its central prediction is concrete: in youth with treatment-resistant aggression, response to clozapine should track the severity and refractoriness of aggression rather than the underlying diagnosis, and its advantage over other antipsychotics should be confined to that refractory stratum. A diagnosis-dependent response, or an advantage spread uniformly across severity levels, would count against the framework.

## 10. Future Directions

The resulting research agenda is straightforward: the proposal must be tested prospectively. That means cross-diagnostic trials that enroll young people by severe, treatment-resistant symptom dimension, powered to detect response across domains and to show that clozapine does something other broad-spectrum agents do not. Five lines of work should surround such trials: consensus work to define treatment resistance for aggression, affective symptoms, suicidality and self-directed harm, and catatonia in youth, without which dimensional trials cannot be designed or compared; multicenter pediatric comparisons of clozapine with current second-line strategies that measure function and not symptoms alone; prospective cohorts and registries with pediatric-specific adverse-event phenotyping;

pharmacokinetic and pharmacogenetic studies that account for ancestry and sex to guide dosing; and implementation research on shortening time-to-initiation through shared care across child psychiatry, pediatrics, nursing, and pharmacy. Some of this groundwork is already being laid. The CLEAR trial is a multicenter randomized comparison of clozapine with other antipsychotics in young people aged 12–24 years with treatment-resistant schizophrenia in real-world settings, with completion expected in 2027 [61,146], which should deliver the first contemporary controlled pediatric effectiveness data in this field and a template for the dimensionally designed studies advocated here.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/futurepharmacol6040057/s1, Document S1: Representative prompts used during generative AI-assisted preparation of the manuscript.

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