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THERAPY IN PRACTICE

Seizure Associated with Clozapine: Incidence, Etiology, and Management

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Abstract Seizures are a known adverse effect of clozapine therapy. The literature varies on incidence rates of seizures, secondary to varying time frames in which each seizure occurred. Tonic-clonic seizures comprise the majority of seizures experienced secondary to clozapine use, but it is imperative to recognize the potential variety of seizure presentation. The exact etiology of clozapine-induced seizure is unknown. Conflicting reports regarding total oral dose, serum concentration, dose titration, and concomitant medications make it difficult to identify a single cause contributing to seizure risk. Following seizure occurrence, it may be in the best interests of the patient to continue clozapine treatment. In this clinical situation, the use of an antiepileptic drug (AED) for seizure prophylaxis may be required. The AED of choice appears to be valproate, but several successful case reports also support the use of lamotrigine, gabapentin and topiramate. Well-designed clinical trials regarding clozapine seizure prophylaxis are lacking. Given clozapine's strong evidence for efficacy in the treatment of schizophrenia and schizoaffective disorder, every attempt to manage side effects, including seizure, should be implemented to allow for therapeutic continuation.

Key Points

Clozapine is associated with an increased risk of seizure with several identified etiologic risk factors. Total oral dose, serum concentration and pharmacokinetic/pharmacodynamic interactions may contribute to seizure risk. Preliminary pharmacogenetic risk factors are also reported. Data are conflicting regarding the rate of dose titration.

Seizure is not a contraindication to clozapine therapy. Antiepileptic drugs can be used to prevent or treat clozapine-induced seizures. Valproate appears to have the most published support, to date. Although fewer studies are available to support their use, gabapentin, topiramate, or lamotrigine may also be viable options in select patient populations.

1 Introduction

A reduction in seizure threshold secondary to antipsychotic use has been a concern since the introduction of chlorpromazine for management of psychosis in the 1950s [1]. Since then, investigations revealed that most antipsychotic drugs impact the seizure threshold. Risk of seizures is a concern associated with all atypical antipsychotics, but appears to be of highest concern with clozapine [2–5] (See Table 1). Atypical antipsychotics with similar chemical structure to clozapine, such as olanzapine and quetiapine, have also demonstrated increased seizure risk [5]. Strong data to guide practitioners in managing patients who experience clozapine-induced seizure are lacking. This

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Table 1 Rates of antipsychotic-induced seizure

Antipsychotic	Incidence of seizure (%)	Comments/references
First-generation		
Chlorpromazine	0.5 % <1,000 mg	[67]
	9 % 1,000 mg or more	
Haloperidol	<1 %	Considered to be low risk [68]
Second-generation		
Aripiprazole	0.1 % adult oral vs. 0 % in placebo	[69]
	0.2 % pediatric oral	
	0.2 % adult IM injection	
Asenapine	0.3 vs. 0 % in placebo	[70]
Clozapine	5 % 1 year rate	High association greater than 600 mg/day [6]
	3.5 % crude rate during trial	
Iloperidone	0.1 vs. 0.3 % in placebo	[71]
Lurasidone	0.1 vs. 0.1 % in placebo	[72]
	No seizures in bipolar studies	
Olanzapine	0.9 %	[73]
Paliperidone	0.22 vs. 0.25 % in placebo	[74]
Quetiapine	0.5 vs. 0.2 % placebo	[75]
Quetiapine XR	0.05 % (1/1,866) vs. 0.3 % (3/928) placebo	[76]
Risperidone	0.3 %	[77]
Ziprasidone	0.4 %	[78]

IM intramuscular, *XR* extended release

paper will discuss the rate of clozapine-induced seizure, describe the types of seizures associated with its use, discuss the risk factors associated with clozapine-induced seizure, and outline the antiepileptic agents used to manage these seizures. In addition, this paper will provide a commentary and evaluation of antiepileptic drug (AED) choice when concern for a clozapine-induced seizure arises, as well as clinical scenarios affecting the appropriate selection of an AED.

We reviewed English-language MEDLINE/PubMed articles containing the keywords "clozapine" and "seizures", "clozapine" and "antiepileptic". Articles evaluating risk of seizures were included. Articles, including case reports, discussing the combination of clozapine and antiepileptics for the management or prophylaxis of seizures were also included.

2 Incidence of Clozapine-Induced Seizures

A review of the literature describes the relative likelihood for which clozapine-induced seizures may occur. Table 2 lists the seizure incidence rates described in the literature. As stated by the manufacturer, seizure is estimated to occur in association with clozapine, with a cumulative 1-year risk of approximately 5 % [6]. This estimation was derived secondary to the occurrence of one or more seizures in 61 of 1,743 patients exposed to clozapine during its clinical testing prior to domestic marketing in the USA [6]. Clozapine-related seizures have been evaluated in several studies, representing varying degrees of incidence: 4–6 % [7] to 20 % [8], up to 22 % [9]. Of note, reported seizure incidence rates vary according to the time frame described in the literature.

Table 2 Incidence of clozapine-induced seizure based on duration of use

References	Description of time period of clozapine use	Incidence (%)
Conca et al. [7]	Not specified	4–6
Devinsky et al. [1]	3.8 years	10
Devinsky et al. [1]	12 weeks	2.9
Kohlrausch et al. [9]	2–96 months	22
Liukkonen et al. [12]	Not specified	9.4
Malow et al. [13]	5 months–5 years	17.5
Novartis Pharmaceuticals Corporation [6]	1 year	5
Welch et al. [8]	Not specified	20

Perhaps the most widely cited studies pertaining to clozapine-induced seizures come from Devinsky et al. [1, 10]. In their first study, 41 out of 1,418 patients managed with clozapine experienced at least one generalized tonic-clonic seizure [1]. This translates to an estimated incidence of 2.9 %. This statistic was further expanded to calculate a cumulative risk, determining that the likelihood of a patient

experiencing a generalized tonic-clonic seizure during 3.8 years of treatment is 10 % [1].

Further investigation of seizure recurrence found that within the approximately 1.3 % of patients who experienced a generalized tonic-clonic seizure during the first 6 months after marketing, 33.8 % of these patients re-experienced a second generalized tonic-clonic seizure when continued on clozapine [10]. However, the majority of patients (78.3 %) were able to continue clozapine therapy without experiencing additional seizures following a decrease in total dose, slower dose titration, or addition of an antiepileptic [10]. This is an important fact to keep in mind, as many patients warrant continued clozapine maintenance despite experiencing a seizure during its use.

3 Types of Seizures Experienced Secondary to Clozapine

Possible explanations for the varying incidence rates may stem from a lack of a consistent definition of "seizure". While the data most heavily present tonic-clonic seizures, there is also evidence to suggest the possibility of additional types of seizures.

3.1 Tonic-Clonic (Generalized)

Tonic-clonic seizures appear to be the most common form of seizure manifesting secondary to clozapine use [8, 11–14]. The likelihood of experiencing a tonic-clonic seizure differs, with literature presenting incidence ranges from 1.3 % [15] to 2.8 % [1], and up to 6 % [11]. Of the types of seizures experienced, tonic-clonic seizures comprised a wide range: 17.5 % to approximately 70 % of cases [8, 13, 14]. Possible explanations for the inflated number of tonic-clonic seizures in proportion to other types of seizures come from inexperience of the evaluator in diagnosing or rating the seizure. Myoclonic seizures could be mistaken for tonic-clonic seizures, thereby falsely elevating the incidence rate of tonic-clonic seizures [11].

3.2 Myoclonic/Atonic (Generalized)

Secondary to tonic-clonic seizures, myoclonic (and atonic) seizures are the next most reported types of seizures resulting from clozapine use [8, 12, 14]. The incidence is approximately 25 % [12] or 27 % [14] to 42.8 % [8] of seizure cases. An estimated 2 % of patients on clozapine will develop myoclonus, usually first presenting in the orofacial region [4, 16, 17]. Special attention needs to be placed on presentation of myoclonus as there is evidence that these symptoms place the patient at increased risk of experiencing a subsequent myoclonic seizure or secondary grand mal seizure [2, 8, 12, 14, 18–21]. Further evaluation must be performed if an individual presents with these symptoms because tardive dyskinesia may also present with abnormal movements in the orofacial region, as well as myoclonic jerks, tics, chorea, and/or dystonia [3]. It may be prudent to evaluate the patient with an electroencephalography (EEG) if tardive dyskinesia is not suspected [8]. Myoclonic seizures tend to occur earlier in treatment during dose titration [22]. Slowing the dose titration and more conservative dosing of clozapine may help minimize the risk of myoclonic attacks and subsequent seizure [4, 19]. Recognition of these myoclonic attacks, or "myoclonic jerks", is imperative as early supportive measures may offset a secondary seizure. Although, orthostatic hypotension and dizziness are commonly experienced by those receiving clozapine, it would be prudent to further investigate the presence of myoclonic or "drop attacks" to differentiate a fall caused by low blood pressure versus a fall secondary to a seizure.

3.3 Simple and Complex Partial Seizures

Clozapine also induces simple or complex partial seizures [8, 14, 23, 24]. It is reported that approximately 6 % of clozapine-induced seizures are considered to be partial [14, 25]. Other sources suggest that the risk may be higher, up to 28.6 % [8]. However, this higher incidence rate may be secondary to selection bias.

Symptoms of these partial seizures may present differently in patients. A published case report presents a patient who experienced visual and auditory hallucinations secondary to partial seizures of the temporal lobe origin [23]. While this may only exist as an isolated case report, it emphasizes the importance in monitoring for seizure, including nontraditional manifestations of seizure sequelae.

3.4 Absence

Although not nearly as common as tonic-clonic seizures, two case reports describe absence seizures in patients controlled on clozapine [12, 26]. Freedman et al. [26] describe a 15-year-old patient taking clozapine 550 mg/day who initially presented with right eye blinking, sialorrhea, postblinking nausea, and a "spacey feeling" that would last for several seconds. These episodes increased in frequency and duration. An EEG confirmed absence seizures. The absence seizures resolved with a decrease in total clozapine dose and did not require an antiepileptic medication.

A second case describes a 34-year-old patient on clozapine 700 mg/day experiencing a grand mal seizure with absence attacks, which was eventually controlled with clonazepam 2 mg/day. Thirteen months following the initial attack, the patient experienced another grand mal

seizure [12]. An absence seizure secondary to clozapine overlooked by providers or caregivers as a seizure is a problem that may lead to underreporting of incidence rates.

4 Risks for Clozapine-Induced Seizures

It is the manufacturer's recommendation that caution be exercised when initiating clozapine treatment in patients with a history of seizures or other predisposing risk factors for seizures such as CNS disorders, other medications that lower seizure threshold or alcohol abuse [6]. One should exercise caution in these situations. However, a history of seizures, including clozapine-induced seizures, is not a contraindication to treatment with clozapine. In fact, case reports of effective use of clozapine in patients with epilepsy exist within the literature [27, 28]. If a patient does experience a seizure while on clozapine, a careful evaluation of the patient's medical record must take place [25]. There is much interest in identifying patient characteristics that place a patient at additional risk for seizure. The following subsections discuss various factors putting a patient at increased risk for experiencing a seizure while on clozapine.

4.1 EEG Abnormalities Prior to Experiencing a Seizure

EEG changes may serve as a predictor of a subsequent seizure, thereby functioning as a warning warranting a decrease in clozapine dose [8]. EEG irregularities may present themselves with antipsychotic use, such as that with clozapine and olanzapine. However, there appears to be an increased risk of EEG changes in patients with comorbid hypertension, bipolarity, and increased age (older than 40 years) [29]. Yet, there is some evidence to suggest that clozapine-induced EEG changes may be more prevalent in younger individuals [30]. Given these conflicting findings, it may be prudent to exercise caution if EEG changes do present.

Additionally, total daily clozapine dose has been associated with increased risk of EEG changes [31]. Although there does not appear to be an exact threshold dose, those greater than 300 mg/day are associated with EEG changes [8, 30].

4.2 Total Oral Dose

Per the product's prescribing information, the risk of seizure is dose related [6]. While there may indeed be a causative relationship between clozapine dose and incidence of seizure [1], a consensus threshold dose is lacking. Clozapine doses greater than 600 mg/day have traditionally been accepted as a clinical cutoff due to increased risk of seizures beyond that dose [11, 15, 24, 32]. Upon further review of the literature, seizure occur in doses as low as a minimum dose threshold of 300 mg daily [12, 14, 24, 33]. Conversely, a review of documented cases of clozapine-induced seizure failed to show a statistically significant relationship between mean clozapine dose and percentage of patients experiencing seizures [31]. While seizures have occurred at higher doses of clozapine (i.e., doses >600 mg/day), seizures still occur at lower doses. This should prompt providers to recognize additional risks to seizures, despite a patient's clozapine dose.

4.3 Clozapine Serum Concentrations

High serum levels, above 1,000 ng/mL (3 μmol/L), have been associated with increased risk of adverse effects, including seizure, confusion, and delirium [34]. Perhaps one of the most cited articles on the topic of clozapine serum concentration and seizures comes from the work of Simpson and Cooper [35], where a threshold level of 1,300 ng/mL (3.9 μmol/L) was identified with two case reports of seizure. An additional case report described a clozapine serum concentration of 1,300 ng/mL (3.9 μmol/L) that resulted in a seizure. The patient was re-challenged, and remained seizure free and stable on clozapine 800 mg with a serum concentration of 700 ng/mL (2.10 μmol/L) [36].

Khan and Preskorn [24] evaluated the relationship between concentration and corresponding seizure rate, and predicted that a level of 2,855 ng/mL corresponded with a greater than 20 % risk of seizure, assuming a linear relationship between concentration and percentage risk. An additional study evaluated corresponding risk and found that serum levels greater than 750 ng/mL (2.25 μmol/L) increased the risk of seizure by five times, after adjusting for age and dose [37].

This risk has led to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatre (AGNP) stating that therapeutic drug monitoring is strongly recommended because overdosing of clozapine increases seizure risk [38]. However, cases of clozapine-induced seizure appear at much lower serum levels in the literature. Freudenreich et al. [11] presented three patients who experienced seizure at therapeutic levels at approximately 200–300 ng/mL (0.6–0.9 μmol/L). Therefore, it becomes difficult to accurately adjust therapy when there is a lack of clear evidence identifying a risk cutoff for seizures [39]. Additionally, there is evidence to suggest that there may be no correlation between serum concentration and risk of seizures [40]. This proposes the hypothesis that there are likely additional factors contributing to seizure etiology in clozapine-induced seizures.

Several factors may alter clozapine concentration thereby predisposing a patient to seizure occurrence. Gender may affect the pharmacokinetic properties of clozapine. Females have approximately one-third higher

serum concentration than men [24]. Older individuals, patients 45–54 years old, have higher concentrations than younger patients [41]. In general, however, gender and age variables are not likely to increase seizure likelihood [1] despite the propensity for contributing to increased serum concentrations.

4.4 Rapid Dose Titration

Current clozapine dosing guidelines recommend that it be slowly titrated to limit the risk of adverse effects, including orthostasis, respiratory depression, and seizures [15, 32, 42]. Historically, a slow titration has been adopted as standard of practice for these reasons, but there is a lack of strong evidence to insinuate that rapid dose titration will precipitate a seizure. The most cited explanation for this caution comes from Devinsky et al. [1], who reported seizures occurring in eight patients who received rapid titration of clozapine (i.e., increased more than 200 mg within 2 weeks). However, more recent studies argue that rapid titration of clozapine may not be a risk factor. In a naturalistic cohort study of rapid clozapine titration, patients ($n = 111$) received 25–100 mg as needed every 6 h on the first treatment day, followed by 25–100 mg/day titration. None of these patients experienced seizure or other serious adverse events despite rapid dose titration [43]. Ifteni et al. [44] further investigated the same rapid titration schedule in patients with bipolar disorder ($n = 44$) and found that only two patients required discontinuation of clozapine (for hypotension and excessive sedation). While evidence may exist cautioning against rapid titration to prevent other adverse effects, such as respiratory depression, the evidence for caution in preventing seizures via this method is not as convincing.

4.5 Concurrent Medications

Agents known to lower seizure threshold should be used with caution or avoided in patients with prior medical history significant for seizures. Moreover, using combined agents that individually increase the risk of seizure should be done so with great caution. Reports of seizures resulting from co-administration of clozapine with erythromycin [36], haloperidol [45], and lithium [46] illustrate the higher likelihood of seizure. Special attention should also be given to patients using medications known to interact with the metabolism of clozapine. Much attention has been placed on the importance of monitoring activity involving cytochrome P450 (CYP) isoenzyme 1A2, a major metabolic pathway of clozapine. Measures should be taken to avoid the use of potent CYP1A2 inhibitors, such as ciprofloxacin and fluvoxamine, which could result in toxic serum clozapine concentrations [47, 48].

4.6 Smoking Cessation

Smoking is prevalent amongst individuals with schizophrenia [49, 50], but also causes an induction of CYP1A2. Therefore, if a patient makes the choice to quit smoking, a dose reduction of clozapine will be necessary. Smoking cessation increases clozapine serum concentration by a mean 57.4 % after adjusting for statistical extremes in the sample [51]. McCarthy et al. [52] describe a case in which a patient controlled on clozapine 450 mg and fluoxetine 20 mg experienced myoclonus and subsequent grand mal seizure following smoking cessation. Although not a pharmacologic agent, smoking and smoking cessation have the ability to cause clinically significant changes to CYP1A2 activity that may contribute to seizure risk.

4.7 Pharmacogenomics

Pharmacogenomics may be a factor in predisposing a patient to tonic-clonic seizure, specifically at the cytochrome P450-isoenzyme level. Kohlrausch et al. [9] found a significant association between *CYP1A2*1F/*1F* and increased risk of seizure in patients receiving clozapine ($\chi^2 = 4.526$, $P = 0.033$, odds ratio 2.69, 95 % confidence interval 1.042–6.940). Individuals with two copies of this high-activity **1F* allele may be predisposed to clozapine-associated seizure. *CYP1A2*1C* was not correlated to seizure. This preliminary evidence identifies a possible genetic factor regulating CYP1A2 expression and activity affecting clozapine pharmacologic disposition.

5 Antiepileptics for Clozapine-Induced Seizure

With the somewhat unpredictable nature of clozapine-induced seizures and the fact that seizures can occur in individuals without risk factors, it may seem prudent to utilize pharmacologic prophylaxis with an AED under certain circumstances. However, there is disagreement about whether or not such use is appropriate for primary prophylactic measures [2]. The earliest strategies described in case reports utilized antiepileptic agents as secondary treatment to clozapine in order to sustain antipsychotic therapy despite seizures [1]. Convincing scientific evidence to support pharmacologic antiepileptic management is lacking; however, this is a strategy that allows continued maintenance of clozapine treatment in patients who do not respond to alternative antipsychotics. This section summarizes case report literature covering the use of specific AEDs for preventing and treating clozapine-induced seizures. Table 3 summarizes each case report or case series.

Table 3 Case reports of antiepileptics used for preventing and managing clozapine-induced seizures

References	AED dose (mg/day); treatment or prophylaxis	Age (years); gender	Clozapine dose (mg/day); time to seizure onset	Other medications used	Other info. (misc.)
Divalproex sodium					
Meltzer and Ranjan [55]	750–1,500; treatment and prophylaxis	27; female	300; 15 days	Chloral hydrate as needed, acetaminophen, metronidazole	Patient stabilized on 400 mg clozapine
Guha and Nizamie [56]	Not described; prophylaxis	28; male	325; ~2 months	Diazepam 185 mg	
Foster and Olajide [57]	500–1,000; treatment and prophylaxis	32; female	125; 15 days. Second seizure at clozapine 237.5 mg 3 weeks after first seizure	Fluoxetine 40 mg, zopiclone 7.5 mg	Patient stabilized on clozapine 450 mg, valproate 500 mg, citalopram 20 mg
Gabapentin					
Usiskin et al. [21]	2,100; prophylaxis	15; male. Prophylaxis with gabapentin at age 19	400; 4 weeks	Olanzapine 25 mg, clonazepam 2 mg	First trial of clozapine-induced seizure treated with phenytoin and valproic acid was not well-tolerated
Landry [63]	1,200; prophylaxis	65; female	37.5; ~4 weeks. Dose eventually increased to 300 mg	Haloperidol 10 mg, procyclidine 15 mg	Divalproex was not well-tolerated; second seizure occurred when gabapentin dose was decreased to 600 mg
Lamotrigine					
Muzyk et al. [61]	200; treatment and prophylaxis	20; male	600; 4 days after clozapine dose change. Patient had been on clozapine for "several months"	Lithium 900 mg, haloperidol 5 mg	Clozapine 200 mg corresponded to serum concentrations of clozapine 120 ng/mL and norclozapine 130 ng/mL; past divalproex use associated with neutropenia
Topiramate					
Dursun and Devarajan [64]	125; treatment and prophylaxis	29; male	800; onset not described	None	Weight loss of 21 kg over 5 months caused by AED
Navarro et al. [65]	200; treatment and prophylaxis	23; female	200; 3 weeks	Sertraline 100 mg	Good response to clozapine; clozapine not discontinued at any time

AED antiepileptic drug

5.1 Divalproex Sodium

Most cases of clozapine-induced seizure prophylaxis involve using divalproex sodium (i.e., valproic acid). Some reasons for this include its wide margin of safety and utility for managing various seizure types. There are also reports that when used in conjunction with clozapine, valproate can improve its efficacy for managing psychotic and affective disorders [53] and refractory schizophrenia with cerebellar pathology [54].

Reports of divalproex sodium (i.e., valproate) for managing clozapine-induced seizure describe a variety of situations where the AED successfully managed the seizure, thereby allowing for clozapine to be continued for managing refractory psychosis in the absence of other viable treatment options. An early report describes a 27-year-old female experiencing seizure activity while receiving clozapine 300 mg, but eventually tolerating clozapine 400 mg for chronic schizophrenia while maintained on valproic acid 1,500 mg for clozapine-induced seizure [55]. Concomitant medications, however, included chloral hydrate, as needed, and metronidazole, both of which may have also contributed to seizure. The authors suggest that "…the addition of valproic acid should make it possible to continue the use of clozapine in most patients…". Another early example describes a 28-year-old male with refractory schizophrenia responding well to clozapine 325 mg. The dose was reduced to 250 mg because of seizures, however, with re-emergence of psychotic features. It was decided to start sodium valproate (dose not provided by the authors), whereby continued therapy with a higher dose of clozapine with no recurrence of seizure was achieved [56].

A 32-year-old Caucasian female with refractory, paranoid schizophrenia experienced a first-time seizure when started on clozapine 125 mg/day, fluoxetine 40 mg/day, and zopiclone 7.5 mg/day [57]. After the seizure resolved on its own, clozapine was restarted and titrated to 237.5 mg/day, leading to a second tonic-clonic seizure. When valproate 1,000 mg/day was started, clozapine was again slowly resumed. The patient was stabilized on long-term clozapine 450 mg/day, valproate 500 mg/day, and citalopram 20 mg/day. The authors propose a possible early addition of prophylactic valproate in "high-risk" cases.

A naturalistic point prevalence study in a large urban setting identified the shortcomings of divalproex sodium use in institutionalized patients also taking clozapine [58]. Of 81 patients taking clozapine, nearly half (37; 46 %) were identified as being at "high risk" for seizure. This group was defined as having clozapine plasma blood levels greater than 0.6 mg/L (1.8 μmol/L), or doses at or greater than 600 mg/day, and/or co-prescribed additional epileptogenic medications, including concomitant antipsychotics or venlafaxine, and/or an existing seizure disorder. Identifying only 15 % of patients stabilized on valproate for seizure prophylaxis, the investigators concluded that 76 % of those individuals at the highest risk for seizure were not adequately protected from it (defined as valproate level greater than 50 mg/L). The authors conclude that despite clinicians being aware that clozapine carries a risk of seizures, they decide not to prescribe valproate because of the lack of good evidence demonstrating that its use will actually prevent seizures. Unfortunately, studies using other AEDs are no more promising than those already described for divalproex sodium.

While valproate for clozapine-induced seizure prophylaxis has the most available literature, clinical scenarios exist when valproate may not be the optimal AED. Using valproate carries some risks when used concomitantly with clozapine. There are reports of acute and reversible hepatotoxicity with their combined use [59], increased risk of agranulocytosis [60, 61], and increased risk of myocarditis [62]. Cautious patient monitoring is advised when using both agents together.

5.2 Gabapentin

There are two cases of gabapentin in the literature to manage seizure in clozapine users. One describes the prophylactic use of gabapentin 2,100 mg with clozapine 300 mg, olanzapine 25 mg, and clonazepam 2 mg in a 19-year-old male [21]. When the patient was 15 years old, he experienced his first seizure after 4 weeks of management with clozapine 400 mg/day. Phenytoin and valproic acid were not tolerated to manage seizures. After several years of unsuccessful trials of clozapine alternatives, prophylactic AED therapy was sought for the purposes of re-starting clozapine at age 19. Gabapentin was successful in preventing subsequent seizures while being maintained on clozapine therapy. The authors conclude that gabapentin should be considered for treatment or prophylaxis in patients taking clozapine who are at increased risk for seizures, particularly those who have demonstrated positive response to clozapine.

The second case is a 65-year-old woman whose clozapine addition to haloperidol therapy for a 31-year history of paranoid schizophrenia led to a seizure, resulting in clozapine discontinuation after roughly 4 weeks of dose titration [63]. Divalproex sodium was poorly tolerated by the patient, leading to the choice of gabapentin 1,200 mg prophylactically to haloperidol before re-starting clozapine. The clozapine dose was never increased above 300 mg/day, because of concern over inducing another seizure, and the therapeutic response was poor with an augmentation trial of risperidone. The patient had another seizure, and clozapine was discontinued. Unfortunately, clozapine use described in this case report may not have reached a

therapeutic dose sufficient to manage the patient's symptoms. The case does, however, illustrate that gabapentin efficacy as a prophylactic AED was confirmed at 1,200 mg/day but not at 600 mg/day.

5.3 Lamotrigine

The only case report describing using lamotrigine for clozapine-induced seizure is of a 20-year-old male with chronic schizoaffective disorder and polysubstance abuse [61]. The patient had previously been started on clozapine 600 mg and lithium 1,200 mg. After a dose reduction to clozapine 550 mg and lithium extended release 900 mg following myoclonic jerks, the patient experienced a seizure 4 days later. Clozapine was held while starting lamotrigine 100 mg. Notably, the patient had already been tried on divalproex in the past but developed neutropenia when combined with clozapine; neutropenia resolved when the AED was discontinued. As clozapine was re-started, up to 200 mg, lamotrigine was reduced to 50 mg because of concerns for rash. The patient was discharged from the hospital on the following medication regimen: clozapine 200 mg, lamotrigine 50 mg, haloperidol 5 mg, and lithium 900 mg. After 6 months in the outpatient setting, the patient appeared to be well-maintained on clozapine 550 mg, lamotrigine 200 mg, and lithium 900 mg, and no additional haloperidol was used. The authors conclude that lamotrigine therapy made it possible for the patient to resume the higher and more effective clozapine dose of 550 mg/day. Despite having to dose titrate slowly to avoid rash, lamotrigine is a viable option for patients who may require an AED with clozapine. Lamotrigine is fairly weight neutral and does not interfere with clozapine metabolism.

5.4 Topiramate

There are two cases reporting on the use of topiramate for clozapine-associated seizure. The first case involves adding topiramate 125 mg to clozapine 800 mg in a 29-year-old male experiencing myoclonic jerks in both hands, arms, and shoulders, along with a 45.5-kg weight gain over a 2-year period [64]. Following titration of topiramate from 25 mg to 125 mg daily, the individual noticed improvement in mood, complete resolution of the myoclonic jerks, and 21-kg weight loss over a 5-month period. Topiramate's side effect of weight loss provides an additional advantage over other AEDs for management of clozapine-induced seizures, given that clozapine is associated with significant weight gain.

An additional case report describes topiramate 200 mg used in a 23-year-old female to manage clozapine-induced seizure [65]. The patient was treated with other antipsychotics for paranoid schizophrenia and was subsequently changed to clozapine and stabilized on 200 mg/day. The patient was also taking sertraline 100 mg/day for depressive symptoms. During the third week of clozapine treatment, the patient experienced a seizure. The authors describe the patient doing well after 6 months of clozapine 200 mg taken with topiramate 200 mg, with no recurrent seizure episodes.

5.5 Other

In a study based on data from the Clozaril Patient Management System, other AEDs used to aid in clozapine management after seizure were reported, including phenytoin, phenobarbital, and clonazepam [15]. No reports were found on the use of levetiracetam, oxcarbazepine, tiagabine, or other novel AEDs.

5.5.1 Carbamazepine

Although carbamazepine is used concomitantly with clozapine, it is generally recommended to avoid this AED with clozapine because of an increased risk of neutropenia, thereby complicating clozapine-required monitoring [15]. Furthermore, concomitant use of carbamazepine and clozapine can lead to clinically significant pharmacokinetic drug interactions causing up to a 50 % decrease in clozapine blood concentration [66]. The benefits of using carbamazepine with clozapine are not higher than the potential risk, as there are alternative AEDs that can be used more safely when combined with clozapine.

6 Managing Clozapine-Induced Seizures

Once a patient experiences a seizure from clozapine, it is recommended that clozapine is discontinued for 24 h, then re-started at a lower dose (i.e., half the seizure-initiating dose) with the possible initiation of valproate 500 mg [57]. A thorough evaluation of the patient should be performed. Clozapine serum concentrations should be ordered immediately, if available. An investigation into possible triggers will aid in preventing a subsequent seizure.

It may be prudent to start AEDs prophylactically in those patients who require continued use of clozapine yet have previously experienced clozapine-induced seizures, are taking concomitant medications known to decrease seizure threshold, or require their clozapine dose to be increased beyond 550 mg/day [53].

Choice of AED for clozapine-induced seizure appears to favor divalproex sodium; however, not all patients will tolerate the combination. The literature is not confident in choosing amongst other AEDs; however, novel AEDs can

be tried successfully on the basis of individual patient characteristics and concomitant medications. Table 4 provides some rationale for deciding between various AEDs to be used in continuing or re-challenging clozapine therapy following a seizure. If an AED is initiated, it is important to consider the pharmacokinetic drug interactions that accompany many AEDs (i.e., CYP450 isoenzyme induction) when adding one to an existing clozapine regimen. Pharmacodynamic drug interactions include excessive sedation and weight gain associated with select AEDs.

7 Conclusion

We conducted a literature review on the incidence of seizure associated with clozapine, potential risk factors associated with seizure onset, and pharmacologic management strategies of these seizures. Of all antipsychotics currently available in the USA, clozapine is the only one that carries a black box warning regarding seizure [6]. The literature does, in fact, support that there is an increased risk of seizures with clozapine compared with other antipsychotics, but through our evaluation we found that the defined risk differs based on time frame of use. This finding shows that the risk associated with clozapine is something of a moving target and may be dependent on the actual length of therapy. Tonic-clonic seizures remain the most common occurring type, but it is important to remember that various types of seizure may present while on clozapine therapy, including myoclonic, atonic, partial, and absence seizures.

There has been much discussion on the dose-related effect of decreasing seizure threshold and correlations with serum clozapine concentrations. The threshold dose whereby clozapine becomes associated with an increased risk of seizures is debatable. There is no clear cutoff dose presented in the combined literature. Clinically, most practitioners have adopted a theoretical maximum of 600 mg/day, but the literature presents several cases of seizures occurring at lower doses. The same controversies and uncertainties exist for the ability to predict increased risk of seizure using clozapine serum concentrations. The utility of clozapine serum concentration for the purpose of seizure prevention is debated within the literature, mainly because of the lack of a well-established concentration threshold. It would be a safe assumption that seizure is more likely at higher concentrations (i.e., >1,000 ng/mL; 3 μmol/L), but similar to total oral dose, seizures still occur at lower concentrations (i.e., <300 ng/mL; 0.9 μmol/L). Based on conflicting evidence, clozapine-induced seizures are not solely based on total dose or serum concentration.

Risk of seizures appears to be a blend of various circumstances and cannot be clearly attributed to one single risk factor. Given the uncertainty and somewhat unpredictable nature of clozapine-induced seizures, it may be in the best interests of the patient to provide pharmacologic AED prophylaxis. If a seizure does occur, it is assuring that clozapine can still be successfully continued. The literature

Table 4 Factors to consider in selecting an antiepileptic agent for managing clozapine-induced seizure

Agent	Positive considerations	Negative considerations
Valproate	Largest number of available case reports, although few in total	Thrombocytopenia
		Increased weight gain
Gabapentin	Generally well-tolerated	Limited data
	Few pharmacokinetic drug–drug interactions	Not traditionally a first-line antiepileptic choice in controlling seizures
Lamotrigine	May be useful in augmenting clozapine management of psychosis	Limited data in use for clozapine-induced seizures
		Risk of SJS/TEN if dose titrated too quickly
	May reduce alcohol consumption	
	Generally well-tolerated	
Topiramate	May offset clozapine-induced weight gain	Limited data in use for clozapine-induced seizures
	Mixed data regarding efficacy of psychosis control	May worsen cognitive function
Phenytoin	None	Pharmacokinetic drug interaction resulting in decreased clozapine concentration
Benzodiazepines	May help control co-morbid anxiety or agitation	Limited data
		Increased sedation
		Increased cognitive impairment
		Potential increased risk of respiratory depression
Carbamazepine	None	Increased risk of blood dyscrasias
		Pharmacokinetic drug interaction resulting in 50 % decrease in clozapine concentrations

SJS Steven's-Johnson Syndrome, *TEN* toxic epidermal necrolysis

supports combining clozapine with valproate, but lends itself to the potential of using other AEDs to manage clozapine-induced seizure. Nevertheless, clozapine is noted as the most effective antipsychotic for managing psychotic-related symptoms in schizophrenia and schizoaffective disorder. It would be a disservice to the patient to withhold its use if there is a safe and effective side-effect management strategy by way of using anticonvulsants. Seizure prophylaxis will help to ensure that patients are given an adequate trial of a much needed antipsychotic.

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