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When Can Patients with Potentially Life-Threatening Adverse Effects Be Rechallenged with Clozapine? A Systematic Review of the Published Literature

Peter Manu, M.D.[a,b,c], **Deepak Sarpal, M.D.**[a], **Owen Muir, M.D.**[a], **John M. Kane, M.D.**[a,b,c], and **Christoph U. Correll, M.D.**[a,b,c]

[a]The Zucker Hillside Hospital, North Shore – Long Island Jewish Health System, Glen Oaks, New York

[b]Hofstra North Shore – Long Island Jewish School of Medicine at Hofstra University, Hempstead, New York

[c]Albert Einstein College of Medicine, Bronx, New York

Abstract

Background—Clozapine is widely prescribed for treatment refractory patients with schizophrenia, but its use is limited by potentially life threatening adverse effects. Rechallenge after these complications has been occasionally attempted in patients with severe psychotic symptoms.

Objective—To review the outcome of clozapine rechallenge after potentially life threatening adverse effects.

Methods—Electronic, all-language, literature search (1972–2011) followed by demographic and clinical data extraction. The outcome of rechallenge was considered favorable when the lower bound of the 95% confidence interval (CI) of the proportion of patients who could continue clozapine was >50%.

Results—Altogether, 138 patients (mean age: 36.3 years, 65.7% male, 57.6% Caucasian, virtually all with schizophrenia spectrum diagnosis) underwent clozapine rechallenge after developing neutropenia (n=112), agranulocytosis (n=15), neuroleptic malignant syndrome (NMS) (n=5), myocarditis (n=4), pericarditis (n=1) and lupus erythematosus (n=1). Rechallenge strategies were heterogeneous and not systematically evaluated. Clozapine rechallenge was successful in 78/112 patients (69.6%, CI:60.6–77.4) after neutropenia, 3/15 (20%, CI:7.1–45.2) after agranulocytosis, 5/5 (100%, CI:56–100) after NMS, 3/4 (75%, CI:30–95) after myocarditis, 1/1 after pericarditis, and 0/1 after clozapine-induced lupus. Successfully rechallenged patients were followed for 16–96 weeks. None of the rechallenged patients died.

Conclusions—Although controlled studies are clearly needed, using a priori, confidence interval-based criteria, case reports/series suggest that in refractory patients who benefited from

Corresponding Author: Deepak Sarpal, M.D., Department of Psychiatry, Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, New York, 11004 (dsarpal@nshs.edu).

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clozapine, careful rechallenge can be considered after neutropenia and NMS, but not after agranulocytosis and myocarditis.

Keywords

Clozapine; Rechallenge; Agranulocytosis; Neutropenia; Myocarditis; Neuroleptic Malignant Syndrome

Clozapine, the first atypical antipsychotic, was synthesized in 1958 and brought to the European market in the 1970s as a treatment for schizophrenia that was not associated with the risk of extrapyramidal syndrome seen with phenothiazines and butyrophenones (Stille and Hippius, 1971). Shortly after its introduction in Finland in 1975, 18 patients developed severe neutropenia and 8 of them died (Crilly, 2007), prompting the withdrawal of the drug until the mid-1980s. Its world-wide use followed a landmark study demonstrating its superior efficacy for patients with refractory schizophrenia compared with chlorpromazine (Kane et. al., 1988). Since then, clozapine has remained the gold standard treatment for refractory patients with severe psychotic disorders (McEvoy et. al., 2006; Lewis et al. 2006; Essali et al. 2009). For the past two decades, clozapine has remained the most effective drug for schizophrenia patients who fail to respond to treatment with other antipsychotics, with advantages in terms of burden of psychiatric symptoms, avoidance of hospitalization, potential for social and occupational rehabilitation (Whiskey and Taylor, 2007; Kane and Correll 2010) and healthcare costs (Blieden, et. al., 1998; Davis et al. 2007). It is also important to note that clozapine has been shown to reduce suicidal behavior in schizophrenia (Meltzer et al., 2003).

The clozapine acceptance by patients and the frequency of its prescribing by clinicians have been hampered by apprehension regarding adverse effects with life-threatening potential, notably significant agranulocytosis and neutropenia (Alvir et al.,1993; Gersen, 1994), myocarditis (Merrill et al., 2005; Pieroni et al., 2004; Reinders et al., 2004), cardiomyopathy (Reinders et al., 2004), pericarditis (Crews et al., 2010; Rathore et al., 2007), alveolitis (Arias et al., 2011), pancreatitis (Bayard et al., 2005), hepatitis (Chang et al., 2009), nephritis (Au et al., 2004), colitis (Pelizza and Melegari, 2007), drug-induced lupus erythomatosus (Rami et al., 2006), status epilepticus (Gandelman-Marton et al., 2008), diabetic ketoacidosis and hyperosmolar coma (Cohen and Correll 2009), and neuroleptic malignant syndrome (Miller et al., 1991).

The life-threatening complications of clozapine are produced by pathophysiologic mechanisms that are not well understood. The occurrence of severe neutropenia and myocarditis is not dose-dependent (Alvir et al., 1993; Merrill et al., 2005), a finding suggesting that a direct toxic effect on the hematopoietic bone marrow or cardiomyocytes is unlikely. A genetic vulnerability for clozapine-induced agranulocytosis (Athanasiou et al., 2011) and the possibility that myocarditis is the result of on allergic-like hypersensitivity reaction (Pieroni et al., 2004) have been invoked. According to the package insert, treatment with clozapine is contraindicated in patients with history of clozapine-induced agranulocytosis or severe neutropenia and in patients with hypersensitivity to this drug (Micromedex).

In clinical practice, the discontinuation of clozapine is frequently followed by worsening of psychotic symptoms, functional status and quality of life ((Mathewson and Lindenmayer, 2007; Crews et. al 2010; DasGupta and Young, 1991; Bray, 2008; Silvestrini, et. al. 2000; Ghaznavi et. al. 2008). Advice regarding the risks of rechallenge is often sought by psychiatric care providers. In this analysis, we evaluated the published experience with clozapine rechallenge to identify the type of adverse effect for which a preponderance of

evidence indicates a favorable outcome after clozapine rechallenge. In addition, we sought to identify pharmacological strategies that might help the clozapine rechallenge succeed.

Methods

We searched the literature for all studies that reported cases of patients who were rechallenged with clozapine after developing major adverse reactions during initial treatment with this antipsychotic. A search of the *PubMed* site jointly managed by the U.S. National Library of Medicine and National Institutes of Health for the period of 1972-July 2011 was performed using the search terms “clozapine” and “rechallenge”. Demographic and clinical data were extracted for patients of all ages. Successful rechallenges were defined as those whereby the patient did not redevelop the complication of interest during an interval of time established by the authors of the report. The outcome of rechallenge was considered favorable if the proportion of patients able to continue clozapine treatment after rechallenge had a lower bound of the 95% confidence interval of greater than 50%.

Results

We identified 30 reports reporting on a total of 138 patients in whom clozapine rechallenge was attempted after a potentially life threatening adverse drug effect. The rechallenged group included 112 patients with neutropenia, 15 with agranulocytosis, 5 with neuroleptic malignant syndrome, 4 with myocarditis and one each of drug-induced systemic lupus and pericarditis. Patients were on average 36.3 years old, 65.7% were male, 57.6% were Caucasian, and virtually all patients had schizophrenia spectrum diagnosis. None of the patients died during the reported mean follow-up period of 34.5 (range: 2–104) weeks after clozapine rechallenge. Follow up of successfully rechallenged patients ranged from 16–104 weeks.

Neutropenia

A total of 112 patients were included in 14 reports describing cases rechallenged with clozapine after developing neutropenia during prior clozapine treatment (Table 1). Virtually all studies adhered to the widely held threshold for white cell dyscrasia (white blood cell count <3000/cu mm, absolute neutrophil count <1500/cu mm); however, in two reports (Gerbino-Rosen et al., 2005; Eseonu and Carlson, 2010) the decision to discontinue clozapine was made when the absolute neutrophil count was lower than 1600/mm3. The decision to discontinue clozapine was made on the basis of routine hematological testing. Respiratory infections were described in four patients (Dunk et al., 2006; Silvestrini et al. 2000; Sperner-Unterweger et al., 1998), two cases were concomitantly treated with other medications known to produce neutropenia (Dunk et al., 2006) and fever was present in two cases (Frankenburg et al., 1994; Grohmann et al., 1989).

Patients underwent clozapine re-challenge after a time interval ranging from 1–156 weeks. Seventy-eight of the 112 patients (69.6%; 95% CI, 60.6–77.4) were successfully rechallenged with clozapine and did not subsequently develop a blood dyscrasia (Table 1). These patients were observed for 20–96 weeks while on clozapine. In patients with unsuccessful rechallenge, neutropenia reoccurred within a mean of 4.3 weeks, but the time interval was wide, ranging from 0.9–156 weeks. Of the 34 patients who failed rechallenge with clozapine after neutropenia, 15 (44.1%; 95% CI, 28.9–60.1) went on to develop a more severe dyscrasia that was in the agranulocytotic range during their second exposure to the drug.

During rechallenge, many patients were provided with treatments that have been shown to elevate neutrophil counts. Thirty-five patients were treated with lithium, and all but two

(94.3%; 95% CI, 81.4–98.4) successfully tolerated the rechallenge (Kanaan and Kerwin, 2006; Gerbino-Rosen et al., 2005; Small et al., 2005; Ghaznavi et al., 2008; Safferman et al., 1993; Bray et al., 2008). Eleven patients were given granulocyte colony-stimulating factor (G-CSF) along with clozapine to stimulate the production of neutrophils, and 7 (63.6%; 95% CI, 35.4–84.8) were successfully rechallenged (Dunk et al, 2006; Frankenburg et al., 1994; Joffe et al., 2009; Matthewson and Lindenmeyer, 2007; Sperner-Unterweger et al., 1998).

Agranulocytosis

Fifteen patients had developed agranulocytosis before undergoing rechallenge with clozapine after a time interval ranging from 4–468 weeks. Of these, only three (20%; 95% CI, 7.1– 45.2%) were able to continue treatment with clozapine after rechallenge (Table 2). Two of these patients were observed for 44 and 104 weeks, respectively; the remaining patient was observed for an unspecified amount of time. In the three patients with information, aganulocytosis reoccurred after 4, 4 and 104 weeks, respectively. In two patients who failed rechallenge after agranulocytosis, a less severe neutropenia was observed upon rechallenge, but this still led to clozapine discontinuation. In 9 other cases of agranulocytosis (Safferman et al. 1992), the rechallenge led to the recurrence of agranulocytosis or to leukocytosis, but the time to onset and the severity of the hematological abnormalities was not reported.

Neuroleptic Malignant Syndrome

Clozapine rechallenge after the occurrence of neuroleptic malignant syndrome was successful in all five cases (Table 3). Rechallenge was attempted after a mean of 8.5 (range: 1–36) weeks. There was careful monitoring of serum CPK levels in all of these patients who were followed for 30.6 (range: 16–52) weeks. Two of the cases had significant comorbid neurologic lesions. In one case (Tsai et al., 1995), the patient had received cingulotomies prior to treatment, and another patient had a lesion secondary to a self-inflicted gunshot wound (Chatterton et al., 1996).

Myocarditis

Four patients who developed myocarditis during treatment with clozapine were rechallenged and three (75%; 95% CI, 30–95) were successfully treated with clozapine without further development of major adverse drug effects (Table 3). Successfully rechallenged patients were followed for a mean of 27 weeks (range: 2 weeks to “years”). In one patient myocarditis reoccurred after 1.2 weeks. The likelihood for clozapine-induced myocarditis in all four patients had been considered by cardiologists to be ‘probable’ based clinical presentation, laboratory values, and temporal relationship to introduction and discontinuation of clozapine.

Other Serious Adverse Events

In addition, clozapine rechallenge has been reported in to other patients after occurrence of rare complications of clozapine treatment. In the first case, clozapine was successfully re-introduced after pericarditis, which was determined by a cardiologist to be most likely due to the antipsychotic drug, despite the fact that infectious causes could not be definitively ruled out. This patient was monitored with frequent electrocardiograms and had a follow up echocardiogram at 3 months with no recurrence of pericarditis or other cardiac symptoms (Crews, et. al. 2010). The second case carried the diagnosis of clozapine-induced systemic lupus erythematosus, which remitted fully after clozapine discontinuation. The drug was re-started several years later, with subsequent return of clinical and laboratory evidence of systemic lupus (Rami et. al. 2006).

Discussion

We analyzed data regarding 136 patients rechallenged with clozapine after developing neutropenia, agranulocytosis, neuroleptic malignant syndrome, and myocarditis. The outcome of rechallenge was favorable in 78/112 patients 69.6%, 95% CI, 60.6–77.4) after neutropenia, 3/15 (14.3%, 95% CI, 4–40) after agranulocytosis, 5/5 (100%, 95% CI 56–100%) after neuroleptic malignant syndrome and 3/4 (75%, 95% CI 30–95) after myocarditis. None of the rechallenged patients died. The findings are limited by the inherent biases created by the way in which cases are selected for publication, small sample size, and lack of access to the medical records of the rechallenged patients. Furthermore, without access to clozapine registry data, it is possible that we missed cases of rechallenge that have taken place in clinical practice yet that were not reported in the literature.

A recurring theme in the literature about clozapine rechallenge is that clozapine is a last resort and the only medication that successfully treats treatment-refractory patients with psychotic symptoms. Among the rechallenged cases were patients who interacted more with others, became less agitated, and had no suicide attempts or other self-injurious behaviors when taking clozapine (Szarek et. al. 1997). Others were able to move from institutionalized settings to living independently (Small, et. al., 2005). In the patients in whom clozapine rechallenge was attempted, the psychotic symptoms returned despite treatment with other antipsychotics once the clozapine treatment was discontinued (Mathewson and Lindenmayer, 2007; Crews et. al 2010; DasGupta and Young, 1991; Bray, 2008; Silvestrini, et. al. 2000; Ghaznavi et. al. 2008; Small, et. al., 2005; Grohmann, et. al., 1989; Bray and Reid, 2011; Jayathilake and Singh, 2009; Reid et. al. 2001; Huang, 2000; Anderson and Powers, 1991; Goates and Escobar, 1992).

The acceptability of rechallenge after clozapine-induced neutropenia has been enhanced by the commercial introduction of G-CSF preparations. It is clear that G-CSF seems to significantly decrease the length of agranulocytosis and of hospitalization, and therefore should, at least in patients with ANC<500/mm3, be administered within 48 hours (Chengappa et. al. 1996; Gersen et. al. 1994). However, there is no agreement on whether to use G-CSF in cases of agranulocytosis alone, or if it could also be beneficial in cases of neutropenia (Gerson, 1994). The optimal indication, dosage, frequency and duration of administration during clozapine rechallenge have all not been formally evaluated.

The evidence supporting lithium co-prescription with clozapine upon rechallenge is limited to a retrospective case analysis of 25 patients, in which lithium was associated with a 4% rate of repeat blood dyscrasia, which was significantly less than the 21.2% previously reported without lithium co-prescription (Kanaan and Kerwin, 2005). It has been suggested that the milder neutropenias sometimes seen in clozapine treated patients could be due to benign ethnic neutropenia, which is present in 25–50% of people of African descent (Kelly et al. 2007). Lithium might be useful in keeping the WBC counts higher in these patients to avoid the discontinuation of clozapine due to benign ethnic neutropenia that might be confused with a clozapine-induced white blood cell dyscrasia. However, there are concerns that lithium might mask impending agranulocytosis, making the combination potentially dangerous (Whiskey and Taylor, 2007).

Nevertheless, in all but two of the 34 cases with neutropenia who were prescribed lithium in addition to clozapine during the rechallenge, clozapine could be continued. This 94.5% success rate was even higher than after administration of GCS-F, although it is possible that GCS-F was given to patients with more severe neutropenia. In any case, the success rate was only 41.5% in those patients who received neither lithium nor GCS-F, suggesting that

lithium co-administration should be strongly considered when planning to rechallenge a patient who developed clozapine induced neutropenia.

The outcome of rechallenge after clozapine-induced agranulocytosis is clearly much worse than that described for patients rechallenged after developing neutropenia. Only a small minority of 20% could be rechallenged successfully. The reasons for the discrepancy are not entirely clear, but non-modifiable genetic factors appear to be important (Athanasiou et al. 2011; Mcknight et al., 2011). For example, in a large U.S. study, neutropenia leading to discontinuation of clozapine was significantly more prevalent in African-American than in Caucasian patients (5.3% vs 2.4%), but agranulocytosis developed only in Caucasians (Kelly et al., 2007). The genetic control of proteins related to reactive oxygen clearance systems correlates with the susceptibility for clozapine-induced agranulocytosis (Yang et al., 2011) and may influence the increased rate of cell death described after exposure to clozapine plus peroxidase-peroxide preparations (Tschen et al., 1999).

A justified concern expressed in the literature about white cell dyscrasia associated with clozapine treatment is the high frequency of co-prescription of other potentially bone marrow-suppressing medications, and the possibility that the observed leucopenia may in fact be due to these concurrently administered medications and not due to clozapine. Certain medications, specifically valproic acid, may increase the risk of neutropenia (Imbarlina et. al., 2004). Other possible causes of neutropenia with clozapine co-administration include carbamazepine, olanzapine, ibuprofen, chlorpromazine, triamterene, quetiapine, and clonazepam (Dunk et. al., 2006; Wu, et. al. 2008). Furthermore, it is also possible that the combination of two drugs is responsible for a blood dyscrasia that might not have developed with monotherapy of either of the two agents.

The outcome after NMS was surprisingly good. All 5 patients were successfully rechallenged and slower titration seemed to be the only specific strategy that was employed. This high success rate upon rechallenge is in contrast to the potentially life threatening nature of NMS, but seems to point to risk factors that can be transient and that might include overly rapid clozapine titration. Moreover, the diagnostic boundaries between NMS due to antipsychotics and malignant catatonia that may be unrelated to antipsychotic treatment remain somewhat unclear (Lee, 2010).

The outcome of clozapine rechallenge after myocarditis was favorable in 3 out of four cases. However, due to the small number of reported cases, our arbitrarily set threshold of at least 50% success at the lower bound of the 95% confidence interval was not met. Therefore, at a minimum, more case reports in this area are needed to be able to more conclusively assess the ratio of success vs. lack of success before making cautious recommendations in the absence of larger and controlled observations. Finally, we only found one published case each of rechallenge after clozapine-associated pericarditis and lupus erythomatosus and no case reports of rechallenge after diabetic ketoacidosis/hyperosmolar coma or other rare, but potentially life threatening complications.

In conclusion, based on this review of literature, we recommend that in patients with a good response to clozapine for whom no other treatments are effective that clozapine rechallenge be considered after neutropenia (absolute neutrophil count >500/cu mm) and after neuroleptic malignant syndrome. In these patients, an important consideration when weighing the risks and benefits of rechallenge with clozapine is the severity of the hematological abnormality that might occur during rechallenge as well as the severity of the psychiatric illness that is not addressed without clozapine use. Clozapine rechallenge should not attempted in patients who had developed agranulocytosis. Frequent laboratory testing is required because the rechallenge-associated neutropenia or agranulocytosis occur faster and

are more severe than during the initial treatment with clozapine (Dunk et. al., 2006). We suggest that complete blood counts be performed twice each week for at least 3 months after the rechallenge. Time to rechallenge, speed of titration and total dose have not been shown to influence the hematological outcome, but need further study. Similarly, after NMS, frequent monitoring of muscle stiffness and vital signs is mandatory in order to pick up warning signs of recurrence. Whether patients could be rechallenged after myocarditis remains unclear, as the 75% success rate is clearly encouraging, yet due to the small number of reported cases, the lower bound of the 95% confidence interval for success was below 50%. Future studies, including carefully designed prospective trials, should more systematically assess clozapine rechallenge outcomes in severely psychotic patients who have substantial benefits from clozapine that are unmatched by any other available antipsychotic.

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Table 1

Clozapine Rechallenge After Neutropenia

Study	n	Age (years)	Sex	White (%)	Diagnosis	Clozapine treatment (wks)	Neutropenia	Rechallenge Strategy	Time to Rechallenge (wks)	Time to Recurrence (wks)	Successful rechallenge	Follow-up (wks)
Dunk et al., 2006	52	34 (median)	37M, 16F	77	Schizophrenia (refractory)	44 (median)	WBC <3000, ANC <1500	*	35	5.5 (median) 1–156 range	32	96
Kanaan and Kerwin, 2006	24	34 (mean)	14M, 10F	25	Schizophrenia spectrum disorders (refractory)	201 (mean)	WBC <3000, ANC <1500	Li 700 mg/d for 168 wks (avg); Li level 0.54 mmol/L (avg)	*	N/A	24	20
Gerbino-Rosen et al., 2005	20	*	*	*	schizophrenia spectrum, Bipolar, IED, PDD, MDD + psychosis (%not provided)	*	*	7 rechallenged pts also treated with Li	*	0.9	11	44
Joffe et al., 2009	5	26–43 (range)	4M, 1F	*	Schizophrenia	8.98	WBC <3000, ANC <1500	Add-on G-CSF 0.3–0.9 mg/week	70.8	6.5	3	7.8
Sperner-Unterweger et al., 1998	1	17	1M	*	Schizophrenia, mental retardation	56	WBC 2870; ANC 1260	G-CSF 300 mcg doses and decreased dose of clozapine	8	N/A	1	32
Frankenburg et al., 1994	1	50	1M	100	Schizophrenia	108	WBC 1980; ANC 1009	Li 600mg/day; Vit C 1000mg/day	12	4	0	4
Mathewson and Lindenmayer, 2007	1	27	1M	0	Schizophrenia (refractory)	4	WBC2200; ANC 1500	Biweekly G-CSF 300mcg	2	8	0	8
Mathewson and Lindenmayer, 2007	1	42	1M	0	Schizophrenia (refractory)	28	WBC 4400; ANC 1600	G-CSF 300mcg/week	1	N/A	1	20
Wu et al., 2008	1	40	1M	0	Schizophrenia (refractory)	5	WBC 1930; ANC 876	d/c Olanzapine	3.4	N/A	1	44
Ghaznavi et al., 2008	1	55	1M	0	Schizophrenia	624	ANC 1620	Li 300mg/day	>104	N/A	1	24
Eseonu and Carlson, 2010	1	56	1M	0	Schizophrenia	*	*	Li 300 mg/day	104	N/A	1	*
Grohmann et al., 1989	1	48	1F	*	Schizophrenia (refractory)	6	WBC 2900; ANC 1600	Flupentixol decanoate	4	2	0	2
Bray, 2008	1	23	1M	0	Schizophrenia (refractory)	--	WBC 3800; ANC 1400	Low dose Li	156	N/A	1	24
Silvestrini et al., 2000	1	29	1F	*	Schizophrenia (refractory)	156	WBC 2600; ANC 1340	Clomipramine 150 mg/day	20	N/A	1	32
McKnight et al., 2011	**1**	**33**	**1F**	**1**	**Schizoaffective disorder (refractory)**	*	**WBC 2800; ANC 600**	*	*	**N/A**	**1**	**56**
Total	**112**	**37.8 yrs**	**67.7%**	**57.1%**	**>90% SCZ-spectrum**	**110.6 (4–624)**			**37.8 wks (1–156)**	**4.3 wks (0.9–156)**	**69.6%**	**29.6 wks (2–96)**

*= Unknown from text; N/A = not applicable

Table 2

Clozapine Rechallenge after Agranulocytosis

Study	n	Age (years)	Sex	White (%)	Diagnosis	Clozapine treatment (wks)	Neutropenia	Rechallenge Strategy	Time to Rechallenge (wks)	Time to Recurrence (wks)	Successful rechallenge	Follow-up (wks)
Safferman et al., 1992	9	39.2 ± 12.5	5M, 4F	*	*	24.4	WBC <3000; ANC <500	*	4 – 468	Quicker onset; numbers not provided	0	*
Small et al., 2005	1	45	1F	0	Schizophrenia, Mental retardation	312	WBC 1800, ANC 230	Haldol decanoate; Li	10	N/A	1	104
Kanaan and Kerwin 2006	1	27	1M	1	Schizophrenia (refractory)	4	WBC <3000; ANC <500	Li titrated up to 800mg qhs	6	4	0	4
Safferman et al., 1993	1	45	1F	0	Schizoaffective disorder	29	WBC 2400; ANC 357	Li 900 mg qhs prior to rechallenge	5	N/A	1	44
Juul Povlsen et al., 1985	1	53	1M	*	*	52	2900 WBC; ANC 340	*	12	104	0	104
Dunk et al., 2006	1	*	*	*	*	*	*	*	*	4	0	*
Tourian and Margolese (2011)	**1**	**41**	**1F**	**1**	**Schizophrenia (refractory)**	*	**ANC 200**	*	*	**N/A**	**1**	*
Total	**15**	**41.7 yrs**	**50%**	**50%**	**100% SCZ-spectrum**	**84.3 wks (4–312)**		**100% Lithium**	**8.25 wks (4–486)**	**37.3 (4–104)**	**20%**	**64 wks (4–104)**

* = Unknown from text; N/A = not applicable

Table 3

Clozapine Rechallenge After Neuroleptic Malignant Syndrome

Study	n	Age (years)	Sex	White (%)	Diagnosis	Clozapine treatment (wks)	Rechallenge Strategy	Time to Rechallenge (wks)	Time to Recurrence (wks)	Successful rechallenge	Follow-up (wks)
Tsai et al., 1995	1	35	1F	1	Schizoaffective disorder	*	Slow titration of clozapine	1	N/A	1	*
Huang, 2001	1	34	1F	0	Schizophrenia	364	Titration of 250mg over 2 weeks	2	N/A	1	52
Anderson and Powers, 1991	1	26	1F	1	Schizophrenia	5	*	2	N/A	1	24
Goates and Escobar, 1992	1	29	1M	*	Schizophrenia (refractory)	0.5	Titration from 25 to 500 over 2–3 weeks	1.5	N/A	1	*
Chatterton et al., 1996	1	49	1M	1	Schizophrenia (refractory)	40	*	36	N/A	1	16
Total	**5**	**35 yrs**	**40% Male**	**75%**	**100% SCZ-spectrum**	**102 wks (0.5–364)**	**100% Tiration**	**8.5 (1–36)**	N/A	**100%**	**30.6 wks (16–52)**

* = Unknown from text, N/A = not applicable

Table 4

Clozapine Rechallenge After Myocarditis

Study	n	Age (years)	Sex	White (%)	Diagnosis	Clozapine treatment (wks)	Rechallenge Strategy	Time to Rechallenge (wks)	Time to Recurrence (wks)	Successful rechallenge	Follow-up (wks)
Reinders et al., 2004	1	*	*	*	*	*	*	40	N/A	1	*
Jauathilake and Singh, 2009	1	42	1M	*	schizophrenia	1.5	Frequent troponin, CRP levels; weekly echocardiograms	2	1.2	0	2
Reid, 2001	1	23	1M	*	Schizophrenia (refractory)	5	Cardiac monitoring	104	N/A	1	“years”
Bray and Reid, 2011	1	43	1M	*	Schizophrenia (refractory)	2	Serial troponin levels 3x/wk for 6 wks; frequent echocardiograms for 1 year	*	N/A	1	52
Total	**4**	**36 yrs**	**100% Male**	*	**100% SCZ-spetrum**	**2.8 (1.5–5)**		**48.6 (2–104)**	**1.2**	**75%**	**27 wks (2–52)**

* = Unknown from text; N/A = not applicable