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Comparison of Clozapine Response for Inpatients in the Research Setting Versus Routine Clinical Practice

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Abstract

Objective—This study compares patient characteristics and treatment response between inpatients treated with clozapine in a research setting as compared to those initiated on clozapine during routine inpatient treatment.

Methods—Subjects on clozapine, in clinical trials, were compared with clozapine inpatients receiving routine clinical care.

Results—At baseline, patients in routine clinical practice had more negative symptoms ($P < 0.001$), activation ($P < 0.001$) and greater total Brief Psychiatric Rating Scale (BPRS) scores ($P = 0.022$) than those in the research setting. Routine clinical practice subjects had larger decreases in BPRS total scores ($P = 0.042$) and positive item scores ($P = 0.0005$) compared to research

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subjects. Response to clozapine was observed in 15/85 (18%) research subjects as compared to 60/223 (27%) patients in routine care ($P = 0.09$).

Conclusions—Patients treated in routine clinical practice have more severe baseline symptoms, but experience significantly greater improvements in psychiatric symptoms.

Keywords

Clozapine; Effectiveness; Treatment refractory; Schizophrenia

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Introduction

In order for new antipsychotics to be marketed, the efficacy of these agents must be determined in rigorous placebo-controlled randomized clinical trials. These studies usually evaluate the intended effect of a drug under ideal conditions with small, homogeneous patient samples that may not be representative of the entire population of patients with schizophrenia or psychosis. Therefore, clinical trials may not always generalize and answer the question of effectiveness. While many factors may contribute to the lack of generalization between clinical trials and real-world effectiveness, selection of patients is likely one of the most important factors [1].

Clinical studies generally only enroll and randomize about 15% of the screened subjects [2, 3]. The majority of subjects excluded from clinical trials are excluded for not meeting inclusion and exclusion criteria. Previous noncompliance and refusal to consent are also common reasons for not including eligible patients [2]. Other studies involving patients with schizophrenia have reported that those who are recruited into clinical trials are usually male, younger in age, have a more recent onset of illness and have had fewer previous psychotic episodes as compared to those not enrolled in trials [2, 4–6]. Furthermore, inclusion and exclusion criteria for clinical trials are often written in a manner that permits recruitment of patients who are likely to respond to the study medication, and often exclude subjects with comorbid disorders [7]. Consequently, patients who consent for trials may not be representative of patients treated in routine clinical care [3, 5, 8].

Clozapine is an antipsychotic medication that is shown to be superior to other antipsychotics in treatment resistant schizophrenia [9–12]. Estimates suggest that between 20%–33% of patients with schizophrenia are treatment-resistant [13]. Current guidelines recommend treatment with clozapine after failing multiple trials with other antipsychotics [14–16]

Clozapine is a medication many patients are not willing to take, while others are not suited to take it for various side effect and health reasons. It is also a difficult medication to blind in trials, due to unique side effects and the logistical problems of hematologic monitoring [17]. According to a review of experimental studies of clozapine, less than one-third of clinical trials enrolled at least 50 patients and the majority of trials lasted less than 8 weeks [18]. This literature review suggested that the role of observational studies in the evaluation of clozapine should be reconsidered, as only a small percentage of patients with treatment resistant schizophrenia have participated in rigorous clinical trials. This study compares the

baseline characteristics and treatment outcomes for inpatient populations treated with clozapine in research and real world settings.

Methods

Patient records for this study were included from two existing databases, the Clozapine Authorization and Monitoring Program (CAMP) for the state of Maryland and the Treatment Research Unit (TRU) at the Maryland Psychiatric Research Center, Baltimore, Maryland. The CAMP subjects were treated with clozapine in routine clinical settings throughout the state of Maryland and were not involved with research at any point. The subjects from the TRU were all volunteers recruited to be treated with clozapine in the research setting, however the use of clozapine in this population were under the same auspices and approval methods as the real world subjects from the CAMP data. Approval was granted from the investigational review boards of the University of Maryland and the Department of Health and Mental Hygiene for the state of Maryland. A waiver of informed consent was granted due to the nature of data collection.

CAMP is a program begun in 1990 under direction of the Mental Hygiene Administration in Maryland. Its purpose is to coordinate the prescribing and monitoring of clozapine for people receiving treatment in state-inpatient psychiatric facilities, state-supported outpatient clinics, and through the Maryland Medical Assistance/Pharmacy Assistance Program. CAMP maintains a database of demographic data, diagnosis, Brief Psychiatric Rating Scale (BPRS) scores and medication initiation/termination dates. Patients receiving clozapine through programs monitored by CAMP meet specific inclusion criteria, although a few receive clozapine through a due to significant side effects or intolerability to other antipsychotics. Patients must: (1) have a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of schizophrenia or schizoaffective disorder; (2) have failed 2 trials of antipsychotic therapy from different chemical classes; (3) be judged as treatment-resistant by treating physician; (4) have a total BPRS score ≥ 35 with a score ≥ 4 [moderate] on one positive item (emotional withdrawal, conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content, poverty of thought, or inappropriate affect) (18 item; 7-point scale). Exclusion criteria for clozapine use included a history of drug-induced blood dyscrasia, uncontrolled seizure disorder, white blood cell count < 3500 per mm³, history of a myeloproliferic disorder, or pregnancy.

At the time of the study, the TRU was a 28-bed inpatient research unit dedicated to the study and treatment of people with schizophrenia whose symptoms have not responded to traditional interventions. Referrals to the TRU were accepted for people between the ages 18–65 years old who were diagnosed with schizophrenia or schizoaffective disorder. Patients were required to have persistent psychotic symptoms while taking antipsychotic medications, been medically stable and to have been able to understand and voluntarily consent to program requirements. In order to be labeled treatment-resistant, the 4 following criteria had to be met: (1) Persistent positive psychotic symptoms (item score ≥ 4 on at least 2 of 4 positive symptoms on the BPRS: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content); (2) current presence of at least moderately severe illness as rated by a total BPRS score ≥ 45 on the 18 item scale and a score of ≥ 4 on

the Clinical Global Impression Scale (CGI); (3) Persistence of illness defined as no evidence of good functioning in the previous 5 years; and (4) Medication refractoriness defined as 2 prior antipsychotic treatments (from at least two chemical classes) dosed at 600 mg/day chlorpromazine equivalents without significant symptom improvement. Although subjects in clinical trials had more restrictive requirements for clozapine initiation, such as higher total BPRS score, subjects in the research unit were initiated under the guidelines and monitoring of the CAMP office as well.

This analysis includes all subjects from both programs who were diagnosed with schizophrenia or schizoaffective disorder, between the ages 18–65 years old and started on clozapine between 1992–2002 in an inpatient setting. All subjects in this study met either CAMP or TRU criteria of treatment refractory for clozapine use; no subjects included were initiated on clozapine due to side effects or intolerability issues. Since all patients are from the Maryland state system, patients who were treated in the research setting were excluded from the CAMP database. Each subject had an 18-item BPRS performed at clozapine initiation. In the CAMP data BPRS scores were requested to be performed at baseline, 1 month, 3 months, 6 months, and at 12 months. In the research unit, monthly BPRS ratings were performed. BPRS scores were grouped using the five-factor model proposed by Guy: [19] (1) Positive symptoms, “thinking disorder”—(conceptual disorganization, grandiosity, hallucinations, and unusual thought content); (2) Negative symptoms, “anergia”—(blunted affect, disorientation, emotional withdrawal, and motor retardation); (3) Anxiety/depression—(anxiety, depression, guilt, and somatic concern); (4) Hostility, “hostility/suspicion”—(hostility, suspicion, and uncooperativeness); (5) Activation—(excitement, tension, and mannerisms and posturing).

In this study, baseline and 6 month BPRS ratings were used. Subjects with missing BPRS at 6 month had the 3 month ratings carried forward. 57/280 (20%) subjects in the CAMP data were not included due to having no follow-up BPRS scores recorded. Likewise 24/109 (22.0%) subjects in the TRU data were not included. Lack of BPRS score may be due to subjects discontinuing from therapy due to lack of treatment effect, intolerability, significant side effects, refusal for blood draws, or omission of BPRS being submitted. The reason for BPRS omission was not determinable. Thus, for this study, baseline and 6-month BPRS scores were compared between groups using ANCOVA, controlling for baseline differences. A chi-square analysis was conducted between groups to compare the percentage of patients who responded to clozapine. Response was defined as a 20% decrease in total BPRS with a final score ≤ 35 . A univariate logistic regression analysis was used to examine demographic and clinical variables that were predictive of response in each group. A multivariate model was not used because the low number of responders to the case variables limited its predictive value. All statistical tests were two-tailed with α set at a value of 0.05.

Results

A total of 85 research subjects and 223 routine clinical practice subjects were identified as meeting the criteria and having baseline and follow-up (6 month or LOCF from 3 months) BPRS ratings performed. Demographic data was similar between the groups with respect to age. (Table 1) The racial variation, while not statistically significant ($\chi^2 = 8.37$, $df = 2$, $P =$

0.08), did show the cohort in routine clinical practice did have fewer white subjects and more subjects classified as “other,” compared to the research setting. Also, a significantly greater proportion of females as compared to males were treated with clozapine in the research setting vs. those treated in routine clinical practice ($\chi^2 = 4.75$, $df = 1$, $P = 0.03$).

At baseline, total BPRS scores were significantly higher in clozapine subjects from the CAMP database (61.5 ± 15.4) as compared to those treated with clozapine in the research setting (57.2 ± 12.7) ($t = 2.30$, $df = 306$, $P = 0.022$) (Table 2). Lower negative symptom scores (9.4 ± 3.8) were noted for research subjects compared to routine clinical practice subjects (12.5 ± 5.0) ($t = 5.04$, $df = 306$, $P < 0.001$). Similarly, lower activation scores were also noted for research subjects (8.3 ± 3.3 vs. 10.6 ± 4.4) ($t = 4.30$, $df = 306$, $P < 0.001$). During the 6-month period, real-world subjects had significant greater improvement in total BPRS score ($P = 0.042$) and the positive item subfactor score ($P = 0.0005$) as compared to research patients. (Fig. 1).

Clinical response to clozapine ($> 20\%$ improvement in total BPRS scores and total final score of 35) was observed in 15/85 (18%) research subjects as compared to 60/223 (27%) people treated in real-world settings ($\chi^2 = 2.87$, $df = 1$, $P = 0.09$). In the logistic regression model, no variables predicted response to clozapine in routine clinical practice subjects (Table 3). A trend was found that suggested routine clinical practice subjects with a higher BPRS baseline activation score preferentially respond to clozapine ($P = 0.06$). In the research subject group, females ($P = 0.04$) and younger subjects ($P = 0.04$) were more likely to respond to clozapine treatment.

Discussion

In this study, we found significant differences in baseline symptoms and treatment response between routine clinical practice patients and research subjects treated with clozapine. We observed that treatment-resistant patients initiating clozapine treatment in research settings have significantly lower levels of negative symptoms and activating symptoms as compared to people treated with clozapine in routine clinical practice settings. This is not surprising as people with schizophrenia who have a high degree of negative symptomatology are known to have much lower rates of participation in other activities such as employment and therapy groups [20–22]. They may also have a reduced desire to participate in research programs. Another explanation involves the criteria for treatment-resistance. People recruited for treatment-resistant clinical trials are required to have significant persistent levels of positive symptoms, [23] without criteria for severity of negative symptoms. This is most likely selective against those with primarily negative symptoms.

The observation that routine clinical practice subjects have higher activation symptoms may be due, in part, to the fact that people who exhibit agitation and irritability usually are not regarded as ideal candidates for recruitment onto research units and clinical trial settings. Therefore, a natural selection against these patients may be seen in many clinical trials. Patients with high activation scores in the real world in fact may be good candidates for clozapine treatment due to its superior effects on activating and aggressive behaviors [24].

This may partially account for why high baseline activation scores correlated closely with clozapine response.

We also found patients in routine clinical practice settings had a better response with clozapine, specifically for positive symptoms. One explanation is the higher baseline level of symptoms seen in this population. Previous studies have found that patients with more severe symptoms are more likely to respond to clozapine [25–27]. It is also possible that subjects in the research setting are less likely to respond to antipsychotic treatment. The TRU, along with many other clinical trials with clozapine, use the criteria developed by Kane et al. [23] that require patients to have no evidence of good functioning in the previous 5 years. Patients in the CAMP data base were required to meet criteria to be treatment refractory but do not have the same longitudinal requirement of persistent poor response to antipsychotic treatment. Therefore, while higher BPRS ratings were seen in subjects in the routine clinical practice, this may reflect a difference in recent behavior such as non-compliance with medication or recent substance abuse (behaviors which would exclude subjects from the research unit) and not specifically more treatment refractory subjects.

This study does have a several limitations. First, we did not have access to serum blood levels, so we cannot assume that all patients were at or above the therapeutic threshold. Since patients in the real world actually responded more robustly than in the clinical trial setting, the possibility of a type I error is low. Second, it is possible the ratings in the routine clinical practice setting may be biased due to the fact CAMP monitors clozapine usage. However, no subject was refused initiation or requested to discontinue clozapine, based solely on their BPRS score, during the study time. Also, not all BPRS ratings were performed by raters who were deemed reliable, in the TRU raters were required to show consistency between raters ($ICC, > 0.8$), as is standard practice in clinical research settings. While state employed psychiatrists were required to attend training on BPRS ratings prior to achieving authorization to prescribe clozapine in this population at the time of this study, we can not definitively determine what percentage attended training. Information about concomitant medications and side effects was also not available. Clozapine treatment in the research setting was exclusively used as monotherapy, while in the real-world setting other antipsychotics may have been prescribed. While this was discouraged by the CAMP office, we cannot guarantee that antipsychotic polypharmacy did not contribute to favorable response. This limitation may be mitigated by the fact that published data does not demonstrate robust effectiveness with antipsychotic polypharmacy [28, 29]. A related issue and strength of this study, however, is that all subjects regardless of being prescribed clozapine through the CAMP database or TRU had similar criteria for receiving and maintaining clozapine treatment.

Several other factors have also been reported to predict clozapine response including degree and response to extrapyramidal side effects [30, 31], age of onset of symptoms [30, 32], and having the paranoid subtype of schizophrenia [25,30] Since this data was not available for this study we do not know how the groups differed in respect to these attributes.

While clozapine is superior to other antipsychotics in terms of efficacy, it does cause severe and limiting side effects including agranulocytosis, seizures, metabolic disturbances, and

myocarditis [33]. Understanding the factors in research subjects and patients in routine clinical practice that are associated with clinical efficacy may lead to more precise use of clozapine and improve the outcomes of treatment refractory patients with schizophrenia.

This work provides evidence that differences in patient characteristics and outcomes exist between subjects in clinical trials versus routine clinical practice. Differences in the ability of people to consent for research studies and sampling differences may lead to important limits on the generalizability of findings from clinical trials involving the seriously mentally ill. Subjects in routine clinical practice may have more severe symptoms but also may be more likely to respond to treatment.

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Fig. 1.
Mean change in symptoms between groups over 6 months

Table 1

Demographic variables for people treated with clozapine

Variable	Research setting (<i>n</i> = 85)	Routine clinical practice (<i>n</i> = 223)	Statistics
Mean age (mean $\pm$ SD)	38.1 $\pm$ 8.6	38.8 $\pm$ 9.0	$t = 0.57$, $df = 306$, $P = 0.57$
Race	29/85 (34%) Black 56/85 (66%) White	80/208 (38.5%) Black 112/208 (54%) White 16/208 (7.5%) Other	$\chi^2 = 8.37$, $df = 2$, $P = 0.08$
Sex	52/85 Male (61%)	164/222 Male (74%)	$\chi^2 = 4.75$, $df = 1$, $P = 0.03$

Table 2

Mean BPRS scores at baseline and endpoint

BPRS scores	Research setting baseline (<i>n</i> = 85)	Routine clinical practice baseline (<i>n</i> = 223)	Research setting endpoint (<i>n</i> = 85)	Routine clinical practice endpoint (<i>n</i> = 223)
Total	57.2 ± 12.6	61.5 ± 15.4 ^a	46.2 ± 11.6	44.9 ± 14.0
Positive symptoms	18.2 ± 4.2	18.1 ± 5.2	14.9 ± 4.8	12.8 ± 4.0
Negative symptoms	9.4 ± 3.8	12.5 ± 5.0 ^b	8.3 ± 3.4	9.8 ± 4.0
Hostility symptoms	11.1 ± 3.7	10.9 ± 4.0	7.9 ± 2.9	7.3 ± 3.4
Anxiety/Depression symptoms	11.6 ± 4.2	10.7 ± 4.4	9.2 ± 3.7	8.4 ± 3.7
Activation symptoms	8.3 ± 3.3	10.6 ± 4.4 ^c	6.8 ± 2.5	7.3 ± 3.5

All results reported as mean ± SD

^aVersus research setting baseline total (*t* = 2.30, *df* = 306, *P* = 0.022)^bVersus research setting baseline negative symptoms (*t* = 5.04, *df* = 306, *P* < 0.001)^cVersus research setting baseline activation symptoms (*t* = 4.30, *df* = 306, *P* < 0.001)

Table 3

Logistic regression for variables predictive of clozapine response

Variable	Research setting (<i>n</i> = 85)				Routine clinical practice (<i>n</i> = 223)			
	Odds Ratio	95% CI	χ^2 (<i>df</i> = 1)	<i>P</i> -value	Odds ratio	95% CI	χ^2 (<i>df</i> = 1)	<i>P</i> -value
Age (Years)	0.90	0.82–0.99	4.28	0.04 ^a	0.99	0.95–1.04	0.08	0.77
Race: White	1.80	0.41–7.88	0.6	0.44	1.00	0.49–2.05	<0.001	0.99
Male	0.23	0.06–0.92	4.33	0.04 ^b	1.48	0.64–3.42	0.82	0.37
Baseline positive symptoms	0.91	0.74–1.13	0.71	0.40	1.00	0.91–1.09	0.01	0.92
Baseline negative symptoms	0.63	0.23–1.74	0.81	0.41	0.95	0.70–1.29	0.12	0.99
Baseline hostility	1.15	0.90–1.47	1.17	0.28	0.99	0.86–1.10	0.07	0.79
Baseline anxiety/Depression	0.87	0.72–1.05	2.19	0.14	1.04	0.96–1.14	0.91	0.34
Baseline activation	0.90	0.67–1.19	0.57	0.45	0.90	0.81–1.00	3.56	0.06 ^c

^aYounger patients more likely to respond

^bFemales more likely to respond

^cTrend for higher activation scores more likely to respond