ANNALS OF CLINICAL PSYCHIATRY 2013;25(2):125-134

RESEARCH ARTICLE

A case series of clozapine for borderline personality disorder

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BACKGROUND: Borderline personality disorder (BPD) is a common, debilitating disorder for which the evidence base for treatment is modest. This case series aimed to explore preliminary evidence of clozapine's effectiveness for patients with severe BPD.

METHODS: We examined the case notes of 22 female inpatients with a primary diagnosis of BPD who had started treatment with clozapine. Baseline routine clinical data were extracted from the records and at 6 monthly intervals thereafter, up to a maximum of 18 months after starting treatment. Patients also were interviewed about their experiences.

RESULTS: We found evidence for a beneficial effect of clozapine across several clinical domains. Symptom severity, need for enhanced observations, use of additional medication, and the number of aggressive incidents all significantly improved after clozapine. The greatest improvements appeared within the first 6 months of initiating treatment. There also was a significant increase in weight.

CONCLUSIONS: The results suggest that clozapine, with suitable health monitoring, may be beneficial for this clinical population. Larger, randomized, blinded, and controlled prospective studies are needed to confirm these findings.

KEYWORDS: antipsychotic, clozapine, borderline personality disorder, emotionally unstable personality disorder, treatment, pharmacotherapy

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INTRODUCTION

Borderline personality disorder (BPD) is a serious mental disorder characterized by pervasive instability of affect, self-image, behavior, and relationships.[1] It affects up to 6% of adults, commonly young women.[2] Patients experience high levels of psychiatric and physical morbidity, in particularly high rates of self-harm behavior.[3-5] BPD patients make extensive use of mental health services, accounting for a significant proportion of all psychiatric admissions.[6] Women are less likely than men to be admitted to secure mental health services; however, those who are admitted are more likely to be diagnosed with a primary personality disorder, especially BPD.[7] Typically these women experience profound symptoms, with high levels of aggression directed at themselves and others. This group of women present significant therapeutic and risk management needs at considerable personal and societal cost.

Treatment guidelines for BPD vary internationally,[8-11] and although the psychosocial model has dominated, many patients are prescribed multiple medications, often simultaneously, off-label, and at high doses with uncertain benefit. Aside from a small number of high-quality studies,[12,13] the lack of pharmacological evidence to inform clinical practice recently was highlighted.[8,14] More recently, clinicians have been challenged to develop and evidence effective treatments for personality disorders.[15]

Aside from a small number of case reports,[16-18] 5 studies have investigated clozapine for BPD. All reported improvements, whether in affective and psychotic symptoms, global functioning, self-harm behavior, use of emergency tranquilization, or psychological treatment.[19-23] However, the studies are criticized for being retrospective, small, mixing community and inpatient samples, failing to characterize the baseline, lacking structured ratings, lacking serum level or side effect data, or failing to follow-up patients for sufficiently long.

The aims of this case series review were:

- to identify whether clozapine can alleviate symptoms in women with a primary diagnosis of severe BPD
- to explore clozapine's tolerability in this group of patients
- to identify themes in the patients' experiences of treatment with clozapine for this disorder.

METHODS

Participants

The case series sample was drawn from all female inpatients age 18 to 65, with a primary diagnosis of BPD who were inpatients at St. Andrew's Healthcare between January 2002 and July 2010 and were treated with clozapine. St. Andrew's is a specialist secure psychiatric hospital in Northampton, United Kingdom. Its Women's Service has >100 inpatient beds. Psychiatrists consider clozapine for women with severe BPD, who are assessed to be at high risk for engaging in self-harm or aggression to others, and who have responded poorly to other medications and interventions in the past. We included all women who had started clozapine, whether they were still taking it or not and whether they were still inpatients or not. Exclusion criteria included a learning disability (IQ <70) and diagnosis of schizophrenia or other psychotic disorder. The study review was approved by the local Research Ethics Committee (ref: 11/EM0042) and every patient who took part gave their written informed consent, after receiving a full verbal and written description of the study protocol.

Data collection

Demographic and clinical data were extracted from the patients' medical records (**TABLE 1**). Clinical diagnoses were established by each patient's consultant psychiatrist in collaboration with their full multi-disciplinary team, using all available data. These sources included clinical interview, inpatient observation, interviews with third-party family and clinical informants, serial mental state examinations, and structured personality evaluation using the Millon Clinical Multiaxial Inventory–III.[24] Extensive outcome data were collected routinely via standard clinical care at baseline, before the women started clozapine, and at 6-month intervals thereafter, coinciding with the multidisciplinary clinical case reviews for up to 18 months after starting clozapine. For the purpose of this review patients were "on" clozapine once they had been taking it for 12 weeks and had discontinued if they stopped it for ≥14 days.

Primary outcomes included the Brief Psychiatric Rating Scale (BPRS),[25] Global Assessment of Functioning (GAF),[26] the number of days on enhanced (1-to-1) observations in the 4 weeks preceding routine assessment, the number of therapeutic sessions (eg, clinical psychology) attended, the count of risk incidents in the 4 weeks preceding assessment (verbal aggression, physical aggres-

sion to objects, against self, and towards others), and their weighted scores using the modified version of the Overt Aggression Scale.[27] Secondary measures included clozapine dose and serum level, other medicines prescribed, body weight, and serum glucose. We also extracted the number and type of side effects reported and reasons for clozapine discontinuation if applicable.

Each participant was interviewed by a research assistant (C.F.) to establish qualitative data regarding their experience of clozapine. A semi-structured interview schedule was developed to explore the experience of clozapine, together with potential problems and side effects. Questions were posed in an open, neutral manner in interviews that lasted between 20 and 45 minutes. Interviews were audio-taped and transcribed for later analysis.

Hypothesis

On the basis of previous data and clinical experience we hypothesized that treatment with clozapine would be associated with:

- reduced frequency and severity of risk behaviors
- reduced severity of symptoms
- improved functioning
- improved nonpharmacological therapeutic engagement
- reduced concomitant pharmacological treatment.

Data analysis

The data was analyzed with SPSS (version 18). Any missing data were accounted for using last observation carried forward. Patient demographics that could act as potential confounders were assessed for significant correlations with outcomes using Spearman test. If an overall effect of time was significant for an outcome variable, subsequent post hoc contrasts between the time points, baseline vs 6 months, 6 vs 12 months, and 12 vs 18 months were completed using repeated measures analysis of variance. Results are given at a significance level of <.05, and <.005 corrected for multiple comparisons.

The qualitative data were subject to a thematic analysis to develop an understanding of the womens' experiences taking clozapine from their narrative accounts. We used the Braun and Clarke[28] analytical process. Two raters (C.F. and G.D.) completed open coding of the narrative identifying basic semantic segments that were combined into themes, with further re-coding following review and discussion.

TABLE 1
Demographic characteristics (N = 22)

Age at clozapine initiation	**Mean (SD)**
	28.2 (7.7)
Months on clozapine	**Mean (SD)**
	26.2 (22.0)
Highest educational achievement	**n (%)**
No qualifications	12 (54.5%)
GCSE/ordinary level	3 (13.6%)
College vocational level	6 (27.3%)
Advanced level	1 (4.5%)
Prior paid work	**14 (63.6%)**
Comorbid Axis I disorder	**n (%)**
None	12 (54.4%)
Posttraumatic stress disorder	2 (9.1%)
Recurrent depressive disorder	3 (13.6%)
Mental and behavioral disorders due to use of alcohol: dependence	2 (9.1%)
Mental and behavioral disorder due to multiple drugs: dependence	1 (4.5%)
Disturbance of activity and attention	1 (4.5%)
Mild mental retardation	2 (9.1%)
Trichotillomania	1 (4.5%)
Past substance misuse history	**15 (78.9%)**
Level of security at clozapine initiation	**n (%)**
Medium	14 (63.6)
Low	7 (31.8%)
Open	1 (4.5%)
Years as inpatient at clozapine initiation	**Mean (range)**
	2.4 (0.1 to 8.5)
Legal status[a]	**n (%)**
37/41[b]	11 (50%)
37[b]	1 (4.5%)
47/49[c]	2 (9.1%)
47[c]	1 (4.5%)
3[d]	6 (27.3%)
Informal	1 (4.5%)
History of previous admissions to secure services	**n (%)**
	18 (81.8%)
Number of antipsychotics prior to clozapine initiation	**Mode (range)**
	3 (1 to 6)

[a]Refer to sections of the Mental Health Act of 1983, the legislation that governs detention of mentally ill person in hospitals.
[b]Court orders warranting transfer to a convicted person to hospital for treatment at the time of sentencing.
[c]Court orders warranting transfer of a serving prisoner from a prison to a hospital for treatment.
[d]Civil order allowing detention of a patient in a hospital for treatment.

GCSE: General Certificate of Secondary Education.

TABLE 2
Outcome measures

Outcome	Baseline (0)		6 months (6)		12 months (12)		18 months (18)	
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)
BPRS score	21	29.4 (21.5 to 37.3)	21	20.0 (14.0 to 26.0)	21	15.3 (9.5 to 21.2)	18	13.5 (7.8 to 19.2)
GAF score	18	21 (14 to 28)	17	19 (14 to 24)	18	20 (16 to 24)	15	22 (18 to 27)
Observations (days enhanced)	22	10.9 (6.3 to 15.4)	22	2.7 (0 to 5.9)	22	1.3 (0 to 3.2)	18	1.2 (0 to 2.7)
Sessions (number attended)	21	34 (25 to 42)	21	47 (37 to 57)	21	44 (35 to 55)	19	41 (31 to 51)
Sessions (% attended)	21	57.3 (44.4 to 70.2)	21	66.8 (56.5 to 77.1)	21	69.2 (58.8 to 79.6)	18	66.1 (53.2 to 79.1)
MOAS score	22	12.2 (6.0 to 18.4)	22	3.6 (0.2 to 7.0)	22	3.5 (0.1 to 6.8)	18	4.6 (0 to 9.8)
MOAS weighted score	22	65.3 (31.4 to 99.5)	22	19.4 (1.2 to 38.2)	22	16.4 (1.3 to 31.5)	18	19.4 (0 to 39.8)
MOAS self-harm score	22	4 (1.4 to 6.6)	22	0.6 (0 to 1.3)	21	0.7 (0.1 to 1.3)	17	0.4 (0 to 0.8)
MOAS self-harm weighted score	22	33.8 (8.9 to 58.7)	22	5.7 (-2 to 13.5)	21	5.7 (-2 to 13.5)	17	3.4 (0.4 to 7.1)

[a]Significant at 0.005.
[b]Significant at 0.05.

BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning; MOAS: Modified Overt Aggression Scale; Sessions: treatment sessions.

RESULTS

Clinical data

Twenty-two eligible women agreed to participate (**FIGURE**). Ten women had a history of other major mental illnesses. All of the women had been admitted previously to other psychiatric hospitals, with 18 previously detained involuntarily in secure psychiatric hospitals; more than two-thirds were detained under criminal legislation provisions. The women had already spent an average of >2 years in secure hospitals before starting clozapine, most in medium security. Every woman previously had been prescribed ≥1 antipsychotic, the mode was 3, some had received up to 6 antipsychotics.

Outcome data

Clinical symptoms decreased significantly after clozapine ($P < .001$) (**TABLE 2**). This improvement was most marked in the first 6 months ($P = .002$). Mean BPRS scores halved from 29 (95% CI, 22 to 37) at baseline to 14 (95% CI, 8 to 19) by 18 months.

The total number and the weighted scores of aggressive incidents significantly decreased over time ($P = .013$ and $P = .017$ respectively), but did not survive correction for multiple testing. The mean count of aggressive incidents fell from 12 (CI, 6 to 18) to 5 (CI, 0 to 10), and the weighted score from 65 (CI, 31 to 100) to 19 (CI, 0 to 40). This occurred between baseline and 6 months ($P = .002$ and $P = .006$), and remained significant at the trend level after adjusting for time ($P = .059$ and $P = .06$ respectively). The count of self-directed aggression also reduced significantly ($P = .026$), from 34 (CI, 9 to 59) to 3 (CI, 0 to 7) by 18 months, again principally in the first 6 months ($P = .022$).

The number of days on enhanced observations decreased significantly after clozapine, most markedly in the first 6 months ($P < .001$). Although therapy session attendance appeared to increase, this was not significant; GAF score did not change.

TABLE 2
Outcome measures (continued)

	Statistical tests				
	Overall test		0 vs 6	6 vs 12	12 vs 18
	P	*F*			
	>**.001**[a]	9.202	**0.00**2[a]	0.015[b]	0.382
	.402	0.809	0.973	0.644	**0.031**[b]
	.001[a]	12.297	<**0.001**[a]	0.432	0.688
	.184	1.672	0.310	0.692	0.63
	.308	1.214	0.123	0.664	0.800
	.013[b]	6.594	**0.002**[a]	0.734	0.592
	.017[b]	6.322	**0.006**[b]	0.388	0.95
	.026[b]	5.766	**0.012**[b]	0.658	0.138
	.035[b]	5.058	**0.022**[b]	0.894	0.159

Effects on use of other medications

The mean dose of clozapine did not change significantly after the first 6 months of treatment ($P = .72$) and was <300 mg/d. The number of patients prescribed other antipsychotics reduced from 19 to 0 in the first 6 months (**TABLE 3**), while the number and cumulative dose of additional "as required" or emergency antipsychotic medication decreased from baseline to 6 months (both $P < .001$). Similarly "as required," emergency anxiolytic medication administrations and cumulative doses declined ($P = .001$ and $P = .018$ respectively).

Monitoring and physical health outcomes

Mean serum levels were between 360 and 430 ng/mL (**TABLE 4**). At baseline, 2 patients (of 19; 10.5%) were glucose intolerant, which increased to 4 at 6 (of 16; 25%) and 12 months (of 17; 24%). Weight increased significantly ($P = .008$) in the first and second 6-month period ($P = .05$ and 0.03 respectively). These results remained significant after adjusting for time. Drowsiness was the most commonly reported side effect, but reduced over time. Other adverse effects included hypersalivation and tachycardia, which lead to 1 discontinuation.

Qualitative data

In total, 20 women were interviewed. Analysis suggested 2 main themes around clozapine's properties.

Clozapine was perceived as facilitative by the women in 3 ways. First, they reported, improved internal symptoms, typically improved mood and inner calm, self-esteem, and reduced thought intensity.

> *"My thoughts are calmer.... Before they were pretty much all over the place and they were a bit strange. Yeah, I was a bit mad and all over the place before, Clozaril* [clozapine] *calmed them down."* (Patient 30)

Secondly, they reported reduced external symptoms, reduced impulsivity and aggression or self-harm, and improved relationships:

> *"My relationships are better now than they have ever been, with staff and the patients...because I'm stable and they aren't worried about what I'm going to say next."* (Patient 24)

Seventy percent of the women noted both improved internal and external symptoms. Some drew an explicit link between these 2 themes and a third, identifying clozapine as facilitative through access to other therapeutic interventions:

> *"...before because my mood was unstable, I ended up being out of therapy because I wasn't achieving or working towards goals.... I'm really stable and I've started applying the skills that we learn in DBT* [dialectical behavioral therapy]*."* (Patient 24)

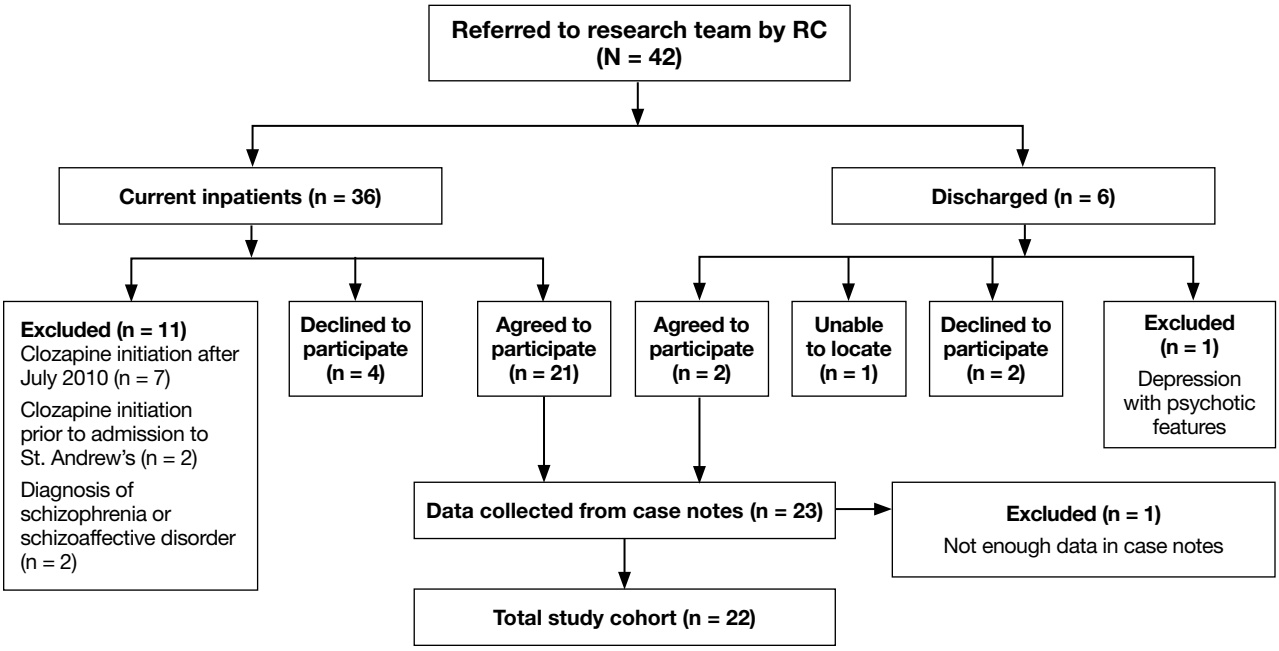
Some participants noted that clozapine was comparatively better than other medications they had been prescribed.

The second theme to emerge was around clozapine's restrictive effects, largely related to accounts of its side effects:

> *"The only reason I came off it was because it makes my heart beat really fast on it and my blood pressure goes up.... It scares me."* (Patient 18)
>
> *"...if being overweight it is what it takes then so be it.... The negative effects are just glitches in a big oil painting."* (Patient 2)

One patient viewed clozapine as restrictive because of its negative effect on the internal and external symptoms of BPD.

FIGURE
Study flow chart



RC: responsible clinician.

CONCLUSIONS

This study represents the largest case series of women treated with clozapine for BPD and the longest follow-up period to date, to our knowledge. It is the first to offer structured clinical outcome data, albeit retrospectively and unblinded, but the first to report on serum levels and tolerability. We believe that the results suggest the presence of a potentially important beneficial clinical effect.

Outcomes

The data revealed clozapine's clinically relevant effect across multiple domains. Symptom severity, number of days on enhanced observations, the use of additional emergency antipsychotic and anxiolytic medication, and the number and severity of aggressive and self-harm incidents all improved.

The greatest improvements were seen early in treatment, a finding consistent with the treatment trajectory of antipsychotics for psychosis.[29-31] The temporal relationship with clozapine initiation—improvement was greatest early on and was sustained—and improvement across multiple subjectively and objectively rated clinical domains suggest a genuine clinical therapeutic effect attributable to clozapine.

An alternate theory is that these effects are the more gradual or coincidental improvements sometimes seen in patients with a personality disorder through the course of inpatient admission.[32] However these women had been in the hospital for 2 years and had failed to stabilize on other antipsychotics before clozapine. Many had been treated with high-dose polypharmacy before clozapine. Indeed, these patients were considered for clozapine because of those treatment failures and in effect were "treatment resistant." Alternatively these effects could be the placebo effect, increasingly seen in psychiatric research.[33,34] However, the women had been treated with other antipsychotics and other medications in the past and did not respond. It could be that clozapine is associated with a more powerful placebo effect, mediated through more intense observation and blood tests. This cannot be excluded in this single compound, retrospective trial.

An alternative prospect is that some of these women—inevitably severe cases—were experiencing "true" psychotic illnesses. In recent years the view that classically

TABLE 3
As required medication

	Baseline (n = 21)	6 months (n = 21)	12 months (n = 19)	18 months (n = 17)	Statistical tests				
					Overall		0 vs 6	6 vs 12	12 vs 18
					P	*F*			
Antipsychotic administered, total count (CI)	27 (17 to 36)	8 (3 to 14)	7 (1 to 13)	4 (1 to 6)	>**.001**[a]	16.75	**.001**[a]	0.425	0.176
Antipsychotic administered, cumulative dose (mg) (CI)	2,725 (1,920 to 3,531)	738 (293 to 1,184)	714 (194 to 1,234)	357 (92 to 622)	>**.001**[a]	24.799	>**.001**[a]	0.926	0.129
Anxiolytic administered, total count (CI)	17 (9 to 26)	5 (1 to 8)	6 (2 to 10)	3 (1 to 5)	**.001**[a]	6.771	**.002**[a]	0.604	0.055
Anxiolytic administered, cumulative dose (mg) (CI)	233 (112 to 354)	48 (5 to 93)	72 (6 to 138)	33 (3 to 64)	**.018**[b]	5.261	**.001**[a]	0.194	0.474

As required, antipsychotic and anxiolytic medication was recorded over the preceding 4-week period at each time point.

Mean total count refers to the mean total number of administrations and the mean cumulative dose refers to mean total dose administered over the preceding 4 weeks and their confidence intervals.

Antipsychotic medication was converted in chlorpromazine equivalents.

Anxiolytic medication was converted to diazepam equivalents.

[a]Significant at $P < .0125$.
[b]Significant at $P < .05$.

defined psychosis is a "fuzzy" construct, commonly found in the general population,[35,36] and with a significant interrelationship with affective and cognitive symptoms[37] has grown. It is impossible, and perhaps irrelevant, to say that these women did not experience brief, time-limited, and in many circumstances, intense psychotic-like experiences.[38] However, these women did not suffer from ICD-10 psychotic disorders such as schizophrenia or bipolar disorder, and clozapine was exerting its beneficial effect outside of those diagnostic constructs.[39]

The results in the context of past studies

Given the clinically complex nature of our cohort, these improvements are important and do not limit the generalizability of the findings. One small study explored the effects of clozapine in inpatients with severe BPD,[22] with a small number of case reports that supported clozapine's beneficial effects, most prominently on self-harming behavior and psychotic-like symptoms.[16-18] Other studies in less severe BPD cohorts have shown improvements in BPRS,[20,40] GAF scores,[20,21,40] "as required" medication,[21] and aggression towards the self[20-23] and others.[20,21] Our study replicates those findings in a larger cohort and over a longer follow-up; the improvements were sustained.

The mechanism by which clozapine could be mediating any beneficial effect in BPD is unknown. Clozapine's advantage in treatment-resistant schizophrenia is well established,[41] but not the pharmacological mechanism. Contenders range across its D1, D2, D4, 5-HT2, and 5-HT6 and γ-aminobutyric acid receptor binding properties.[42] From a more clinical perspective it may be that clozapine is a better anxiolytic than other antipsychotics,[43,44] which is of critical importance in BPD.

Adverse effects

Earlier studies of clozapine failed to investigate its side effect profile. The women in our study gained weight significantly and was cited as a limiting factor and contributed to their decisions about continuation. The rates of weight gain are consistent with findings in schizophrenia[45] where >70% gain weight over 2 years,[46] although the risk may be even greater for women than men.[47] Weight gain for some women in this case series was significant. This is an important consideration given the long-term health burden of excessive weight gain[48] and the signifi-

TABLE 4
Physical measures

	Baseline		6 months		12 months		18 months	
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)
Plasma clozapine (ng/mL)	22	0 (0)	13	430 (200 to 570)	13	410 (290 to 540)	8	360 (280 to 440)
Weight (kg)	22	89.5 (82.2 to 96.8)	22	97.3 (89.0 to 105.5)	22	101.4 (93.1 to 109.7)	17	106.7 (97.3 to 116.2)
Glucose (mg/dL)	19	76.7 (63.0 to 90.9)	16	88.9 (64.6 to 113.0)	17	88.6 (64.3 to 112.9)	14	85.1 (62.6 to 107.6)

cant mortality gap between individuals prescribed antipsychotics and the general public.[49] It may be particularly important in BPD given its association with eating disorders.[50,51]

A number of our patients developed new impaired glucose tolerance over 18 months of treatment. This was lower than is seen in similar studies in schizophrenia.[52,53] Nevertheless, the generally high continuation rates of clozapine in this study (95.5%)—albeit in detained women in whom treatment could be enforced—is consistent with the qualitative data that suggests that many patients consider clozapine's advantages to outweigh its disadvantages.

Limitations

There are methodological weaknesses that limit interpretation of our results. The retrospective nature of the case series, combined with the lack of a control group means that we cannot be sure the effects are attributable to clozapine. Placebo response remains a key limitation for any pharmacological study and may be as high as 70% in BPD.[54] This effect might be even greater for clozapine; however, research in schizophrenia confirm its effectiveness after controlling for monitoring frequency and intensity.[55] Also, patients were not actively participating in research when assessed, except for the later interviews. Furthermore, all of these patients had failed to respond adequately to other forms of pharmacological treatment before clozapine.

Only 22 women of a possible total of 42 agreed to allow examination of their notes for this series. We were unable to determine if patients refused to consent because of problems they experienced on clozapine, either through lack of efficacy or side effects. It is possible that our cohort comprised a subgroup of women who had a positive experience of clozapine, while those who found it ineffective or intolerable refused. Data extracted for this study were collected as part of routine clinical practice by multiple clinicians. Recording practices could have differed in a way we were unable to assess.

This study used the BPRS to rate BPD symptomatology. Data collection for this study began in 2002, before the publication of the Zanarini Rating Scale for Borderline Personality Disorder in 2003,[56] the first dedicated rating scale for BPD symptoms. In its defense, the BPRS is a robust and well validated instrument that has good reliability in the clinical setting.[57] The BPRS was selected because it offers good coverage of the key domains of BPD psychopathology such as mood and emotional arousal, anxiety, and suicidality. Furthermore, by virtue of its ability to index other aspects of psychopathology it allowed us to be confident that these phenomenologically complex patients were not suffering from significant Axis I pathology. Finally, our study does not rely on the BPRS alone and we have presented other clinical indices, including patient report, that corroborate meaningful improvement.

Pharmacological interventions often are used to help patients with BPD. Our preliminary data suggest that clozapine may be useful in helping patients with BPD, at least in those with more severe symptoms. The qualitative data suggested that many women experienced clozapine as more facilitative than restrictive. Our findings do not negate the importance of comprehensive psychosocial interventions, but suggest that clozapine may help when other treatments have failed.[58,59] This therapeutic effect may be direct, through symptom reduction or indirect by means of enabling engagement in other nonpharma-

TABLE 4
Physical measures (continued)

	Test			
	Overall	0 vs 6	6 vs 12	12 vs 18
	n/a			
	0.008	0.05	0.03	0.18
	n/a			

cological treatment. The effect appears within 6 months of treatment. Dosing and serum levels mirror those in schizophrenia, as do side effects. Larger, randomized, blinded, and controlled prospective studies are needed to confirm these findings. ■

DISCLOSURES: Ms. Frogley and Drs. Mitchell, Picchioni, Dickens, and Mason report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. Dr. Taylor has received grant or research support from Bristol-Myers Squibb and Janssen; is a consultant to Servier; and is a speaker for Janssen and Lundbeck.

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