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Is the Time Course of Clozapine Response Correlated to the Time Course of Clozapine Plasma Levels? A One-Year Prospective Study in Drug-Resistant Patients with Schizophrenia

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The relationship between the time course of clinical response to clozapine and the time course of clozapine plasma levels has never been investigated. In the present study, we assessed prospectively the clinical response to clozapine and the plasma levels of the drug and its major metabolites in 32 drug-resistant patients with schizophrenia kept on a fixed dose of 600 mg/day for 1 year Four of the patients met response criteria at week 4 of treatment. At weeks 8, 12, and 24, new responders were 7, 6, and 6, respectively. Nine patients never achieved clinical response. In responders at week 4, clozapine and clozapine-N-oxide plasma levels were significantly higher than in both new responders at weeks 8, 12, and 24 and nonresponders. In new responders at weeks 8, 12, and 24, in spite of a fixed clozapine daily dose, mean drug plasma levels progressively rose up to when clinical response occurred; then, the levels remained stable over time. Nonresponders exhibited mean clozapine plasma levels constantly below the value of 260 ng/ml, with N-demethylation as the preferred metabolic route.The present findings show, for the first time, that the time course of the clinical response to clozapine may be linked to the time course of plasma levels of clozapine and its major metabolites.

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KEY WORDS: *Schizophrenia; Clozapine; Clinical response; Plasma levels*

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Several groups of investigators have assessed the relationships between plasma levels of clozapine and clinical response to treatment. Although effective clozapine plasma level "windows" or response thresholds are still discussed controversially in the literature, the majority of available studies, by using discriminant function analyses or receiver operating characteristic curves, have suggested plasma clozapine concentrations between 350 ng/ml and 420 ng/ml as the optimal break points for predicting response/nonresponse in drug-resistant schizophrenic patients (Perry et al. 1991; Hasegawa et al. 1993; Miller et al. 1994; Potkin et al. 1994; Kronig et al. 1995). Recently, VanderZwaag et al. (1996) reported that the plasma concentration of 250 ng/ml was the clinically ef-

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fective plasma level cut-off. Furthermore, Bender and Eap (1998) described a patient whose clinical response went up and down concomitantly with the increase and decrease of plasma clozapine levels induced by the addition or withdrawal of fluvoxamine. Therefore, it seems that clozapine plasma levels are correlated with therapeutic response.

Clinical studies have shown that the clinical response to clozapine may occur 1 week up to 1 year after treatment initiation (Meltzer et al. 1989, 1990, 1992; Pickar et al. 1992; Stern et al. 1994; Wilson 1996). The reasons for such a variability in the time course of the response to clozapine treatment are not clear. Changes in plasma levels of the drug may obviously be involved. Indeed, plasma levels of clozapine have been found to vary not only between patients on a similar dose, but also intraindividually among subjects on fixed dose regimens over several weeks of treatment (Centorrino et al. 1994a). Therefore, the possibility exists that the different time courses of response to clozapine may be related to different time courses of the drug plasma levels, even when the drug daily dose is kept constant.

In the present study, we prospectively assessed clinical response and plasma levels of clozapine and its major metabolites in a group of drug-resistant schizophrenic patients kept on a fixed dose of clozapine for 1 year, in the attempt to verify whether temporal changes in clozapine plasma levels were associated with the time course of patients' response to the drug.

METHODS

The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 88 subjects) who completed at least 52 weeks of treatment and had complete data records. They were 32 Caucasian subjects, 21 men and 11 women, meeting both DSM-IV criteria for schizophrenia and Kane's criteria for drug-resistance except one patient who did not met the Kane's criterion of duration of illness of at least 5 years (Kane et al. 1988). Their age range was 24–62 yrs (mean ± SD = 34.4 ± 1.1 yrs); the duration of their illness ranged from 2 to 32 yrs (11.9 ± 7.2 yrs). Twelve of them met the DSM-IV criteria for paranoid schizophrenia, 5 for disorganized schizophrenia, 13 for undifferentiated schizophrenia, and 2 for catatonic schizophrenia. All patients provided written informed consent to participate in the study after all the procedures were completely described to them.

In an effort to have consistent baseline conditions, before entering into the study, all the patients' psychoactive drugs except for typical antipsychotics were tapered and discontinued. After patients had been taken on this drug regimen for at least 2 weeks, baseline assessment was completed. Then, clozapine treatment was started with dose increments of 25–50 mg every 2 days to bring patients to the dose of 400 mg/day by the end of the week 2. Patients were taken at this dose regimen up to the end of week 4, when a second clinical assessment was performed. Those subjects meeting the response criteria (see below) were maintained on the 400 mg/day dose regimen up to the end of the study, whereas the remaining patients received further dose increments of 50 mg every 2 days to reach the maximum established dose of 600 mg/day by the end of week 6, and then were kept on this dose regimen up to week 52. Typical antipsychotics were rapidly tapered and discontinued during the first week of clozapine treatment. Clozapine was administered in 2–3 divided (and approximately equal) doses, with the last dose of the day given between 7:00 P.M. and 8:00 P.M. Patients were hospitalized up to the achievement of their maximum clozapine daily dose; then, they were discharged and clozapine was administered at home by staff nurses, who carefully checked patients' compliance up to the end of the study.

Psychopathological assessment was performed by means of the Expanded Brief Psychiatric Rating Scale (BPRS: 24 items and a scoring from 1 to 7) (Lukoff et al. 1986) both before starting clozapine (baseline) and every 2 weeks up to week 52. Patients were a priori defined responders as they attained a 20% decrease in the BPRS total score plus a post-treatment BPRS score of 47 or less. These criteria had to be met at two consecutive rating points; responders were classified as such when they first met a priori criteria.

After 4, 8, 12, 24, and 52 weeks of clozapine administration, blood samples were collected by venipuncture before the morning dose of clozapine (12 ± 1 h after the last dose). Plasma was separated by centrifugation and stored at –20°C until assayed for clozapine, N-desmethylclozapine, and clozapine-N-oxide. At baseline and at the same time points of blood drawing, patients' body weight (BW) was recorded. Plasma levels of clozapine, N-desmethylclozapine, and clozapine-N-oxide were determined by reversed phase HPLC and UV detection, as previously described (Volpicelli et al. 1993).

Results were expressed as mean ± SD and statistically assessed by analysis of variance (ANOVA) with or without repeated measures, post-hoc Tukey's test and χ^2 (Chi-square) test with Yate's correction, where appropriate.

RESULTS

Twenty-three (71.8%) of the 32 patients responded according to the a priori response criteria by 12 months of treatment. Of these subjects, 4 (12.5%) first met response criteria at week 4; 7 (21.8%) were first classified as responder at

Table 1. Demographic and Clinical Characteristics of Patients Classified as Responders and Nonresponders

	All Responders	New Responders at week 4	New Responders at week 8	New Responders at week 12	New Responders at week 24	Nonresponders
Age (yrs)	35.1 ± 11.3	41.5 ± 16.6	34.5 ± 12.7	35.0 ± 12.0	31.6 ± 3.2	36.3 ± 10.5
Age at onset (yrs)	23.3 ± 6.1	25.5 ± 7.5	24.2 ± 8.4	22.5 ± 3.8	21.8 ± 4.9	23.5 ± 5.8
Length of illness (yrs)	11.7 ± 7.6	16.0 ± 11.6	10.2 ± 6.5	12.5 ± 8.8	9.8 ± 4.5	12.5 ± 6.5
Number of previous hospitalizations	4.7 ± 4.7	5.0 ± 5.4	3.0 ± 1.9	6.5 ± 7.2	4.8 ± 4.2	5.3 ± 4.7
Education (yrs)	8.5 ± 3.3	7.2 ± 1.5	9.0 ± 4.0	7.8 ± 2.9	9.6 ± 3.9	8.8 ± 3.2
Males/females	15/8	2/2	3/4	5/1	5/1	6/3

week 8; 6 (18.7%) at week 12; and the remaining 6 (18.7%) at week 24. Nine (27.2%) of 32 patients never achieved clinical response. One-way ANOVA showed no significant difference in the mean age ($F_{4,27} = 0.472$, NS), age at onset ($F_{4,27} = 0.271$, NS), length of the illness ($F_{4,27} = 0.525$, NS), number of previous hospitalizations ($F_{4,27} = 0.445$, NS), education ($F_{4,27} = 0.412$, NS), baseline BMI ($F_{4,27} = 0.933$, NS), and baseline BPRS total scores ($F_{4,27} = 2.518$, NS) between the groups of responders at different time points and nonresponder subjects (Tables 1 and 2). In all groups, Body Mass Index (BMI) progressively increased throughout the study period (Table 2). Two-way ANOVA with repeated measures showed no significant effect for group ($F_{4,27} = 1.04$, $p = .4$) and no significant group × time interaction ($F_{5,135} = 0.44$, $p = .9$), but a significant effect for time ($F_{5,135} = 21.03$, $p < .0001$), indicating that BMI increased over time with no significant differences among the five response groups. Changes in BMI and BPRS total scores over treatment are shown in Table 2. Twenty-five of the thirty-two patients were smokers (18 were responders and 7 nonresponders); the distribution of smokers between responder and nonresponder patients was not statistically significant (χ^2=0.0008, $p = .9$).

Plasma levels of clozapine, N-desmethylclozapine, and clozapine-N-oxide in the different response groups are shown in Figure 1 and 2. As concerns clozapine plasma levels, two-way ANOVA with repeated measures showed significant effects for group ($F_{4,27} = 7.19$, $p < .0001$) and time ($F_{4,108} = 17.60$, $p < .0001$) and a significant group × time interaction ($F_{4,108} = 4.93$, $p < .0001$), indicating that the time course of plasma clozapine concentrations significantly differed in the five response groups. Indeed, in nonresponder subjects, mean (±SD) plasma clozapine levels ranged from 220.1 (±101) to 251.1 (±75.2) ng/ml, were considerably lower than in the other groups, showed only a minimal increase following the enhancement of clozapine daily dose (after week 4), and remained stable throughout the study period. Responders at week 4, instead, exhibited mean plasma clozapine levels ranging from 459.5 (±149) to 473.2 (±198) ng/ml, that were considerably stable from the week 4 to week 52 of treatment. Responders at week 8, 12, and 24 exhibited progressive increases in the mean values of plasma clozapine up to the week when they attained clinical response; then, these values showed only minimal changes up to week 52 of treatment. At the time of the clinical response, mean plasma levels of clozapine were 468.3 (±173) ng/ml in responders at week 4, 588.4 (±136) ng/ml in responders at week 8, 409.4 (±120) in responders at week 12, and 537.8 (±209) ng/ml in responders at week 24. These values were significantly higher than correspondent time point values in nonresponder patients ($p < .001$,

Table 2. BMI and BPRS Total Score Changes Throughout Clozapine Treatment in Patients Classified as Responders and Nonresponders (Mean ± SD)

	Baseline	Week 4	Week 8	Week 12	Week 24	Week 52
BMI (Kg/m^2)						
All responders	27.11 ± 3.55	27.77 ± 3.59	28.05 ± 3.80	28.40 ± 3.75	29.17 ± 3.66	29.60 ± 3.70
New responders at week 4	25.17 ± 1.32	25.91 ± 0.65	26.01 ± 0.68	26.18 ± 0.57	26.64 ± 10.26	26.91 ± 0.69
New responders at week 8	25.60 ± 3.34	26.44 ± 3.42	26.63 ± 3.58	26.96 ± 3.03	28.00 ± 3.48	27.98 ± 3.65
New responders at week 12	28.07 ± 3.35	28.73 ± 3.76	29.23 ± 3.91	29.79 ± 4.63	30.25 ± 4.89	30.84 ± 4.68
New responders at week 24	29.21 ± 4.18	29.63 ± 4.24	29.87 ± 4.56	30.16 ± 4.04	31.17 ± 2.69	32.02 ± 1.98
Nonresponders	26.30 ± 5.84	26.72 ± 5.91	27.22 ± 5.99	27.23 ± 6.04	27.57 ± 5.19	28.15 ± 5.66
BPRS Total Score						
All responders	72.3 ± 14.2	56.3 ± 11.7	52.6 ± 11.8	44.5 ± 10.3	38.2 ± 7.5	37.1 ± 8.2
New responders at week 4	65.2 ± 5.8	42.7 ± 7.8	42.7 ± 7.8	37.7 ± 8.5	35.2 ± 8.5	35.2 ± 6.1
New responders at week 8	71.4 ± 12.9	54.1 ± 5.4	45.4 ± 1.9	40.8 ± 6.3	37.1 ± 8.7	33.2 ± 7.4
New responders at week 12	68.8 ± 6.2	60.3 ± 8.5	56.8 ± 6.6	41.3 ± 6.8	38.0 ± 6.9	36.6 ± 9.5
New responders at week 24	81.8 ± 21.5	64.1 ± 14.5	63.6 ± 14.7	56.6 ± 9.2	41.8 ± 6.7	43.5 ± 6.6
Nonresponders	79.6 ± 21.6	70.8 ± 12.9	69.8 ± 13.6	63.8 ± 11.4	56.5 ± 5.1	62.0 ± 10.9

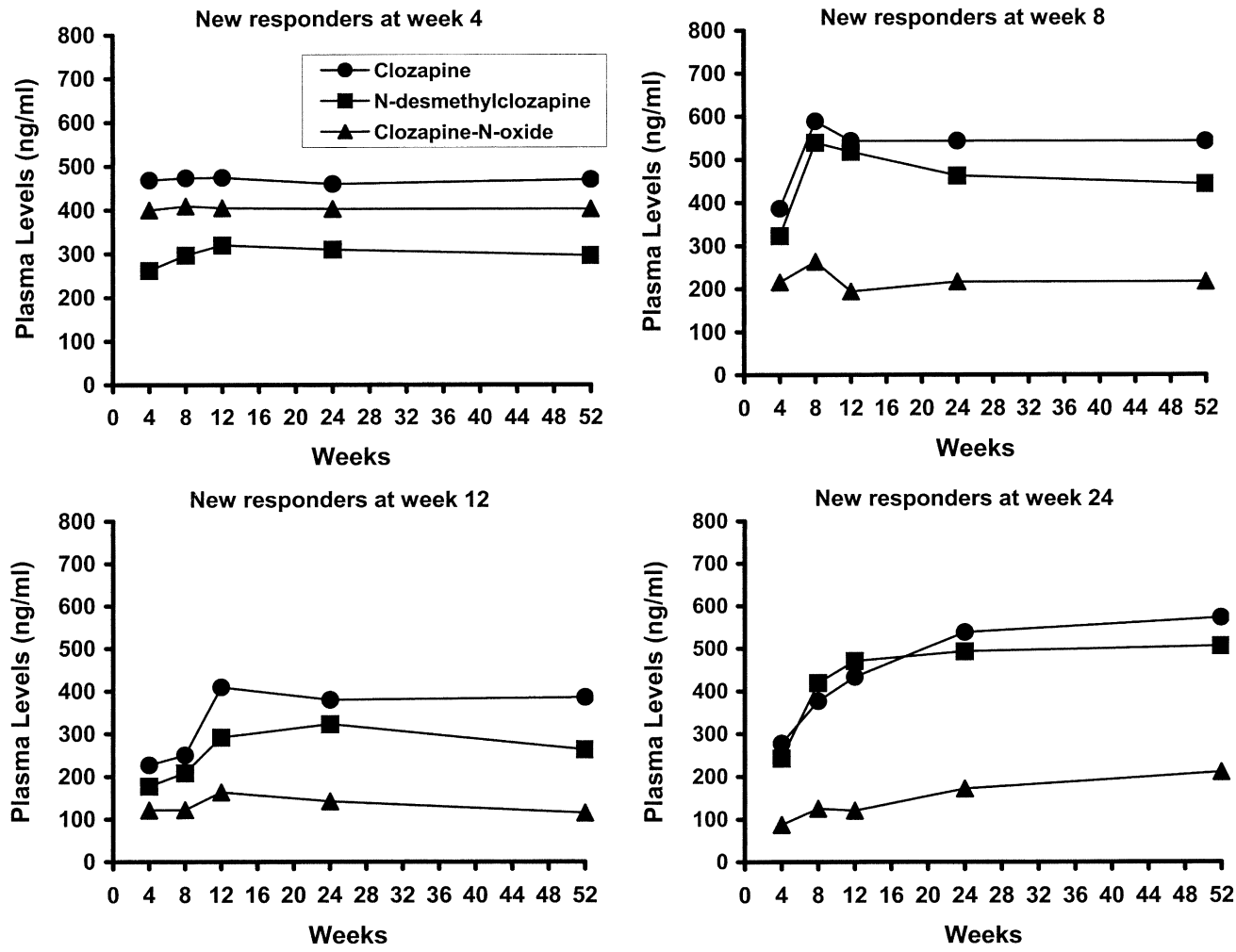

Figure 1. Mean plasma levels of clozapine, N-desmethylclozapine, and clozapine-N-oxide in patients first classified as responders at weeks 4, 8, 12, and 24 over 1 year of clozapine treatment.

$p < .001$, $p < .02$, and $p < .001$ in responders at week 4, 8, 12, and 24, respectively).

As concerns N-desmethylclozapine, two-way ANOVA with repeated measures showed significant effects for group ($F_{4, 27} = 4.23$, $p < .0001$) and for time ($F_{4, 108} = 8.21$, $p < .0001$), but no significant group × time interaction ($F_{4, 108} = 1.53$, $p = .1$), indicating that absolute values of N-desmethylclozapine significantly differed among the groups and showed significant changes over time, although these changes were not significantly different among the five groups (Figures 1 and 2).

As concerns clozapine-N-oxide, two-way ANOVA with repeated measures showed a significant group effect ($F_{4, 27} = 9.46$, $p < .0001$), but no significant effect for time ($F_{4, 108} = 0.49$, $p = .7$) and no significant group × time interaction ($F_{4, 27} = 0.59$, $p = .8$), indicating that, although absolute values significantly differed among the groups, these values remained considerably stable over treatment and their time course did not significantly differ among the five response groups (Figures 1 and 2).

DISCUSSION

The most important aspect of this study is that we prospectively assessed the time courses of both clinical response and plasma levels of clozapine and its major metabolites in neuroleptic-resistant schizophrenic patients kept on a fixed daily dose of clozapine up to week 52 of treatment.

From the clinical point of view, we found a 12-month response rate to clozapine of 71.8%; that is high but consistent with data reported in other follow-up studies (Meltzer et al. 1989; Lieberman et al. 1994; Conley et al. 1997). Our data confirm the results of Lieberman et al. (1994), who suggested that the optimal duration of clozapine treatment for establishing its clinical efficacy, at least in fixed dose trials, is no longer than six months. Indeed, we did not observe further responses after 24 weeks of treatment.

Previous studies aiming to identify plasma concentrations of clozapine that could be regarded as optimal break points for predicting response/nonresponse left

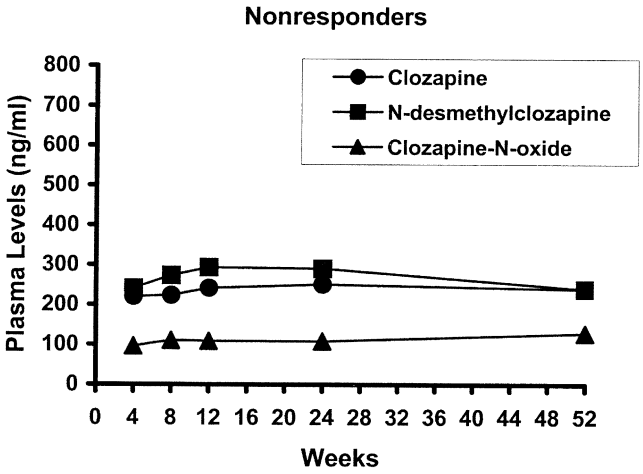

Figure 2. Mean plasma levels of clozapine, N-desmethylclozapine, and clozapine-N-oxide in patients classified as nonresponders over 1 year of clozapine treatment.

unexplained why some patients respond early in the treatment while others do it later. In the present study, we did not aim to identify a clinically effective plasma level cutoff of clozapine, but we grouped the patients on the basis of the time of their clinical response and observed different time courses of plasma concentrations of clozapine and its major metabolites.

In nonresponder patients, mean clozapine plasma levels were constantly below the value of 260 ng/ml and N-demethylation was the preferred metabolic route, which led to N-desmethylclozapine plasma levels even higher than clozapine itself. In the early responders, instead, N-oxidation of clozapine prevailed over N-demethylation; hence, clozapine-N-oxide plasma levels were considerably increased. Both clozapine-N-oxide and N-desmethylclozapine are inactive metabolites (Fitton and Heel 1990); however, as clozapine-N-oxide can be reduced to clozapine whereas N-desmethylclozapine does not (Jann et al. 1994), it is possible to speculate that subjects who preferentially metabolize clozapine via N-oxidation may rapidly achieve higher plasma values of the antipsychotic with a greater therapeutic efficacy. Indeed, at week 4, early responders had mean clozapine plasma levels higher than both nonresponders and responders at week 8,12, and 24. Therefore, it could be argued that the preferential N-oxidation of clozapine may be associated with a faster therapeutic response. The metabolic hypothesis needs, however, to be confirmed in larger studies because, as already reported for haloperidol, subsequent experiments have shown that regeneration of reduced haloperidol back to haloperidol is a very minor pathway in humans (Korpi et al. 1985).

In responders at week 8, 12, and 24, in spite of a fixed clozapine daily dose, mean plasma levels of the antipsychotic progressively rose up to when clinical response occurred; then, they remained stable over time. Mean plasma levels of clozapine, measured at the times of clinical responses, did not significantly differ among the responder groups but were significantly higher than the respective time point values in nonresponder patients. Because in early responders mean clozapine plasma levels were at the maximum value already at week 4 and remained stable over treatment, it could be argued that response to clozapine is linked not only to the achievement of the maximum drug plasma value, but also to a stabilization of this value over time.

Although it is easy to understand the rise in clozapine plasma levels occurring in responders at weeks 8, 12, and 24 after the increase of the clozapine daily dose at week 4, it is not simple to explain the further increase of plasma levels in responders at weeks 12 and 24, when these patients were kept on a fixed daily dose of the drug. Factors known to affect clozapine metabolism (Jann et al. 1993) can be invoked as potentially responsible for these results. None of the patients in our sample, however, received substances known to strongly alter clozapine metabolism, such as anticonvulsants or selective serotonin reuptake inhibitors (Centorrino et al. 1994b; Fabrazzo et al. 2000). Age, caffeine intake, and smoking behavior can be seen as constant variables over the study period and are therefore unlikely to contribute to intraindividual plasma level variability. BW changes were of a comparable magnitude in all groups, and patients' compliance was carefully monitored by staff nurses for the whole study period. The only variable that may be involved in the determinism of these results is gender. Indeed, we had a preponderance of male patients in our late responders. In a previous study (Fabrazzo et al. 1996), we showed that, in patients kept on almost stable daily dose of clozapine for 18 weeks, increases in plasma levels of both clozapine and N-desmethylclozapine occurred from week 6 to week 24 of treatment. We suggested that these increases could be caused by the fact that the percentage of extensive metabolizers of clozapine is high in males, and that part of these extensive metabolizers become poor metabolizers as the treatment goes on, as already described for other antipsychotics (Sakalis et al. 1973; Bergling et al. 1975). In line with this idea, Lin et al. (1994) found that, in a group of 14 male schizophrenic patients on chronic treatment with clozapine, all were poor metabolizers. Therefore, if we speculate that most of our male late responder patients belonged to the category of extensive metabolizers who progressively become poor metabolizers, this might explain our findings. Considerable intraindividual variations in clozapine plasma levels have been reported in samples of patients including prevalently or almost exclusively male subjects and treated with fixed doses of the drug (Centorrino et al. 1994a; Kurz et al. 1998).

This study involved a substantial group of formerly poorly treatment-responsive schizophrenic patients who had been on stable clozapine regimen for 1 year. Our findings show, for the first time, that the time course of

the clinical response to clozapine is correlated to the time course of plasma levels of clozapine and its major metabolites. If confirmed in future studies, these results may provide a possible explanation for interindividual differences in the clinical response to this antipsychotic drug.

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