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LETTER TO THE EDITOR

Effectiveness of clozapine and olanzapine: a comparison in severe, psychotically ill patients

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New atypical antipsychotics have opened a new era in the treatment of schizophrenia owing to their effectiveness both on positive, but especially negative, symptoms, without extrapyramidal side-effects (Tandon et al., 1999). The archetypal atypical antipsychotic is clozapine, whose main side-effect is agranulocytosis. Recently, other new atypical antipsychotics have been developed, such as olanzapine (Stephenson and Pilowsky, 1999), which do not produce any adverse haematological effects (Beasley et al., 1997). Clozapine and olanzapine share lower D2 and D3 receptor affinity in the basal ganglia and nigrostriatal system, and higher affinity to muscarinic (M) and histaminergic (H) receptors than haloperidol. Moreover, clozapine has higher affinity to adrenergic ($\alpha 1$ and $\alpha 2$) receptors, while olanzapine has higher affinity to D2, D3, D4 and serotonergic (5-HT-2A) receptors (ratio 5-HT-2A/D2 > 2) (Coward, 1992). The pharmacological profile can explain the efficacy of these drugs not only on the positive, but also especially on the negative symptoms, representing the originality of new antipsychotic treatment. The improvement of primary negative symptoms (Crow, 1980) and the absence of secondary symptoms (produced by extrapyramidal side-effects) result in an increased compliance (Marder, 1998) and improvement of cognitive functions (insight capacity, self-awareness, judgement) (Meyer-Lindenberg et al., 1997).

The aim of our study was to evaluate the effectiveness of clozapine and olanzapine in the treatment of schizophrenic patients in our psychiatric department. This is constituted by hospital wards connected to community services (outpatient care, semi-residential and residential centres for rehabilitative social programmes).

Subjects and clinical assessments

All patients admitted to our psychiatric wards (Presidio Psichiatrico di Diagnosi e Cura 1) with schizophrenia diagnosis and schizoid personality disorders (according to DSM-IV) (American Psychiatric Association, 1994), and treated with clozapine and olanzapine from September 1995 to September 1998 were selected. Previously these patients had never been treated with these drugs, only with traditional neuroleptics. The sample consisted of 25 patients: 12 treated with clozapine and 13 with olanzapine. In the clozapine group 10 patients were affected by paranoid and 2 by disorganized schizophrenia; in the olanzapine group 4 patients were affected by paranoid, 3 by disorganized, 3 by catatonic, 1 by undifferentiated schizophrenia and 2 by schizoid personality disorder, according to DSM-IV criteria. The sample size was conditioned by the difficulty in selecting patients whose clinical features were similar enough to be compared.

The atypical neuroleptic treatments were evaluated for a whole period of 482.08 ± 29.42 d for the clozapine group and 207.30 ± 30.26 d for the olanzapine group (patients treated for a period less than 30 d were excluded from our study) composed of a period of in-patient care (overlapped for the two groups: 43.3 ± 4.49 d for clozapine, 44.23 ± 4.45 d for olanzapine) and the following outpatient care. The therapeutic dose ranges were: from 250 to 600 mg/d for clozapine and from 10 to 30 mg/d for olanzapine. Clozapine (Leponex, Novartis Farma SpA, Origgio Varese, Italy) and olanzapine (Ziprexa, Eli Lilly, Nieuwegein, The Netherlands) were used. The procedures followed were in accordance with the ethical standards of the Institutional Ethical Committee on human experimentation.

The following clinical features of the sample were analysed: age, diagnosis, previous illness duration, rate of hospitalization and previous neuroleptical treatment (effectiveness, compliance, tolerance and side-effects). Clinical symptoms were assessed by means of Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) at admission and discharge. Social functioning was evaluated by means of the Global Assessment of Functioning (GAF) scale (Spitzer et al., 1979) at admission and at the end of the follow-up period. The rate of the rehospitalization under atypical neuroleptics treatment was evaluated. Moreover, patients' compliance with rehabilitative outdoor programmes under clozapine and olanzapine treatment was assessed at the end of follow-up period. Data were analysed by means of ANOVA, Fisher test and Kruskal–Wallis test, and expressed as mean $\pm$ S.E. (Statistica, Version 5, '97 Edition, Statsoft, Italy).

The two groups were significantly different for mean age (40.75 ± 6.27 yr in clozapine-treated patients,

Address for correspondence: Dr R. Di Lorenzo, Department of Mental Health, Presidio Psichiatrico di Diagnosi e Cura 1, Policlinico Via del Pozzo 71, I41100 Modena, Italy.
Tel.: 0039-59-422232-951 *Fax*: 0039-59-422589 or 0039-59-2055376
E-mail: genedani@unimo.it

Table 1. Influence of clozapine and olanzapine treatments on BPRS score

	Clozapine		Olanzapine	
BPRS score items	Admission	Discharge	Admission	Discharge
Unusual thought content	6.54	4.91*	6.07	4.07*
Suspiciousness	6.00	3.36*	5.54	2.76*
Conceptual disorganization	5.00	2.64*	4.69	2.61*
Distractibility	5.00	2.36*	3.00	1.46*†
Bizarre behaviour	5.91	3.91*	6.46	3.23*
Self-neglect	4.82	2.18*	5.31	2.46*
Hostility	5.54	2.55*	5.93	2.46*
Tension	6.18	2.82*	5.38	3.00*
Anxiety	5.55	3.00*	4.23	2.31
Hallucinations	6.27	4.36*	4.38	3.00
Mannerism and posturing	5.00	3.64	5.15	3.00*
Emotional withdrawal	3.73	2.27	5.38	2.38*
Blunted affect	3.91	2.45	5.15	3.00*

*$p < 0.05$ (at least) vs. admission of clozapine and olanzapine group respectively.
†$p < 0.009$ vs. discharge of clozapine group. Kruskal–Wallis test.

33.15 ± 8.45 yr in olanzapine-treated patients) and previous illness duration (18.58 ± 8.16 yr in the clozapine group, 9.92 ± 8.78 yr in the olanzapine group), but both groups presented the same rate of previous hospitalization, quantified in number of admission/illness days (4.41 ± 4.38 d in the clozapine group, 3.43 ± 2.92 d in the olanzapine group) and similar compliance, effectiveness and side-effects with previous neuroleptical treatments (7 patients in the clozapine group and 9 in the olanzapine group had rarely and irregularly taken the previous therapy; 8 patients under clozapine therapy and 6 under olanzapine therapy did not present any symptomatic improvement, while all others presented only a mild improvement; 9 patients in each group were not affected by important side-effects). Further, at admission, the score of BPRS items was similar for the two groups as well as the GAF scale score.

Our results have shown that at discharge, both clozapine and olanzapine treatments significantly decreased the BPRS score of the following items (Table 1): unusual thought content, suspiciousness, conceptual disorganization, distractibility, bizarre behaviour, self-neglect, hostility, tension.

The score of anxiety and hallucinations was significantly decreased by clozapine therapy, while mannerism and posturing, emotional withdrawal, blunted affect score were significantly ameliorated by olanzapine therapy (Table 1). Only the score of distractibilty was significantly reduced by olanzapine in comparison with the clozapine group (Table 1).

Both drugs significantly reduced the rate of hospitalization during the treatment evaluated as percent of admissions before and under treatment (from 100 to 25% in clozapine group; from 100 to 23% in the olanzapine group, $p = 0.0002$ and $p = 0.0001$, respectively, Fisher test). At the end of the follow-up period, the GAF score of both groups was significantly increased (from 26.66 ± 2.84 to 37.08 ± 1.89 in the clozapine group; from 25.00 ± 3.15 to 46.53 ± 4.09 in olanzapine group, at least $p < 0.005$ ANOVA) but the GAF score of the olanzapine group was significantly higher than that of the clozapine group, in spite of a shorter period of treatment ($p < 0.05$, ANOVA). Moreover, both atypical neuroleptics facilitated the patients' participation in psychosocial rehabilitative programs: 7 olanzapine-treated patients began a semi-residential centre activity and 2 patients again started competitive work; 2 clozapine-treated patients were admitted to residential centres and 2 patients began a social training programme.

Discussion

Our sample was constituted by 'non-responsive' patients, who were affected by a severe psychotic disturbance, as demonstrated by long period of illness, high rate of hospitalization and low GAF score at admission. Either clozapine or olanzapine significantly ameliorated positive symptoms, but only clozapine was effective in reducing anxiety and hallucinations, while olanzapine was more effective in reducing negative symptoms, such as mannerism and posturing, blunted affect and emotional withdrawal. Olanzapine-treated patients obtained signifi-

cantly higher GAF scores than clozapine-treated patients and more frequently participated in rehabilitative programmes (9 olanzapine-treated patients vs. 4 clozapine-treated patients). This result could be due to the difference of age and previous illness period between the two groups: clozapine-treated patients were 7.5 yr older and fell ill 9 yr earlier than olanzapine-treated patients. But the two groups were not significantly different in other clinical features (the rate of previous hospitalization, GAF scale and score of BPRS items) which might have affected the therapeutic efficacy. Finally, the clozapine treatment period was longer than olanzapine treatment but, in any case, we compared clozapine- to olanzapine-treated patients, because we observed an early and dramatic improvement of psychotic symptoms with olanzapine treatment.

In conclusion, even though the two groups were small and not completely comparable, the data suggest that the improvement of negative and positive symptoms, associated with a more tolerable side-effects profile, enhances therapeutic compliance and permits regular therapy that, consequently, prevents relapses. Moreover, olanzapine therapy has surprisingly been shown to be more effective than clozapine in improving social and working skills.

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Rosaria Di Lorenzo[1], PhD, Grazia Tondelli[1], PhD and Susanna Genedani[2], ScD

[1] Department of Mental Health, 'Presidio Psichiatrico di Diagnosi e Cura 1', Policlinico, Via del Pozzo 71, Modena, Italy

[2] Department of Biomedical Sciences, Section of Pharmacology, University of Modena and Reggio Emilia, Via Campi, 287, I41100 Modena, Italy