given ICI 204,636 every 8 hours with stepwise increases in dose from 25 to 250 mg per dose. Serial plasma samples were collected following the morning dose after achieving steady state at 75, 150 and 250 mg per dose to evaluate the pharmacokinetics of ICI 204,636. Five patients (1 man and 4 women) withdrew from the trial but none due to serious adverse events related to ICI 204,636. There were no deaths. Pharmacokinetic parameters were calculated by noncompartmental methods. The mean (± SEM) parameters are summarized below:

Dose (mg)	Group	T_{max} (h)	C_{max}(ss) (ng/ml)	$AUC_{0-8\ h}$(ss) (ng·h/ml)	$t_{1/2}$ (h)	CL/f (L/h)	V_z/f (L)
75	Men	1.0 (0.5–3.0)	277±54	1070±193	NC	89±12	NC
	Wom.	1.0 (0.5–3.0)	294±41	1200±175	NC	86±16	NC
150	Men	1.0 (0.5–4.0)	625±121	2300±334	NC	78±10	NC
	Wom.	1.5 (0.5–4.0)	572±63	2410±339	NC	73±8	NC
250	Men	1.5 (0.5–4.0)	778±108	3380±456	5.8±0.3	87±10	710±93
	Wom.	1.5 (1.0–3.0)	879±72	4080±529	6.6±0.8	72±9	672±116

There were no significant differences among doses in dose-normalized C_{max}(ss) and $AUC_{0-8\ h}$(ss) in both men and women indicating dose proportionality. Additionally, no significant differences were found for any of the parameters between men and women at each dose level. This indicates that there are no gender differences in the pharmacokinetics of ICI 204,636.

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MULTIPLE-DOSE PHARMACOKINETICS OF 'SEROQUEL' (ICI 204,636) IN ELDERLY SCHIZOPHRENIC PATIENTS

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'Seroquel' (ICI 204,636) is a dibenzothiazepine derivative currently in Phase III clinical development as an antipsychotic agent. The primary objectives of this study were to investigate the multiple-dose pharmacokinetics and safety of ICI 204,636 in elderly psychotic patients. Twelve patients aged 63 to 85 years meeting the DSM-III-R criteria for chronic schizophrenia and bipolar disorder entered this trial. After a 2-day washout period, patients were given ICI 204,636 every 8 hours with stepwise increases in dose from 25 to 250 mg per dose. Serial plasma samples were collected following the morning dose after achieving steady state at 100 and 250 mg per dose to evaluate the pharmacokinetics of ICI 204,636. Nine patients completed this trial. Three patients withdrew because of postural hypertension, dizziness or tachycardia. There were no deaths. Steady-state pharmacokinetic parameters were calculated by noncompartmental methods. The mean (± SEM) parameters are summarized below:

Dose (mg)	T_{max} (h)	C_{max}(ss) (ng/ml)	C_{min}(ss) (ng/ml)	$AUC_{0-8\ h}$(ss) (ng·h/ml)
100	1.2 ± 0.28	507 ± 43.1	146 ± 30.1	2130 ± 243
250	1.8 ± 0.26	1080 ± 122	355 ± 45.3	4940 ± 504

Dose (mg)	$t_{1/2}$ (h)	CL/f (L/h)	V_z/f (L)
100	6.2 ± 0.38	51.5 ± 5.92	471 ± 72.9
250	6.8 ± 0.56	54.7 ± 5.23	513 ± 25.8

No significant differences among doses were found for T_{max}, $t_{1/2}$, oral clearance (CL/f) and volume of distribution (V_z/f), and for dose-normalized C_{max}(ss), C_{min}(ss) and $AUC_{0-8\ h}$(ss) values. This indicated that the pharmacokinetics of ICI 204,636 was independent of dose within the dose range studied. Compared to younger patients, the oral clearance (CL/f) in elderly patients was up to 50% lower. This suggests that the clinical effective dose for elderly patients may be 50% lower than that for younger patients.

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DOES PRENATAL INFLUENZA CAUSE NEURODEVELOPMENTAL SCHIZOPHRENIA AND OBSTETRIC COMPLICATIONS?

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At least a dozen epidemiological studies have reported an association between prenatal exposure to influenza epidemics and adult schizophrenia. We studied this association in individual schizophrenic patients, and also investigated its relationship to another postulated risk factor for schizophrenia, obstetric complications. We recorded gestational infections, obstetric complications, gestational age, and birth weight, by interviewing the mothers of 121 DSM-III-R schizophrenic patients using structured instruments. Significantly more infections were reported in the second, compared with the combined first and third, trimesters of the patients' gestations (20/121 vs. 6/121, $p = 0.005$). Influenza accounted for 70% of second trimester infections ($p = 0.004$). Schizophrenic patients whose mothers reported second trimester influenza were almost five times more likely to experience at least one definite obstetric complication ($p = 0.01$), and weighed a mean of 210 g less at birth. Second trimester maternal influenza may impair foetal neurodevelopment and predispose to both obstetric complications and schizophrenia. The pathogenetic mechanism may involve maternal genetic predisposition to autoimmune processes involving cross reactivity between anti-influenza IgG antibodies and embryonic neuronal cadherins.

Gestational infections reported by the mothers of 121 schizophrenic patients with the timing of their occurrence by trimester of gestation.

Infection	Trimester of gestation			Total	p
	1st	2nd	3rd		
Influenza	0	14 (11.6)	2	16 (13.2)	0.004
Respiratory infection	0	4	0	4	0.012
Pyelonephritis	0	2	0	2	0.120
Gastroenteritis	0	0	1	1	1.000
Candidiasis (oral)	1	0	0	1	1.000
Rubella	0	0	1	1	1.000
Dental abscess	1	0	0	1	1.000
Total	2	20 (16.5)	4	26 (21.4)	0.005

OUT-PATIENT TREATMENT IN A MULTIDIMENSIONAL SETTING IN SEVERE SCHIZOPHRENIA — CASE REPORT

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The 30 year old patient has been suffering from paranoid schizophrenia with systematized paranoia and severe affective problems for 11 years. His interpersonal relationships have been impaired by his extreme vulnerability and reduced frustration tolerance as well as by his tendency to dissocial behaviour and alcohol abuse. Since the onset of his illness, he often had to undergo in-patient treatment on a long-term basis.

Only few days after his last dismission in November 1994, rehospitalisation was necessary. Now, for the first time, a basis of mutual confidence could be established which facilitated continuous therapeutic sessions and regular medication which he had strictly rejected before. Thanks to continuous stabilisation and increasing reality testing, he could be dismissed after 6 weeks. During the first three months after dismission, he used our therapeutic setting daily, especially psychotherapeutic sessions and additional ergotherapy and sociotherapy. Gradually, the intensity of care could be loosened, as the patient regained his autonomy step by step.

Considering his complex history with numerous long-term hospitalisations, often against his will, it is encouraging to see that now

in-patient treatment could be abbreviated compared to his previous phases with similar severity of symptoms, without requiring rehospitalisation.

So the vicious circle with lack of reality testing, non-compliance, substance abuse and dissocial behaviour could be broken in favour of a mainly regular way of living under intensive out-patient treatment. The high expenditure of time by the psychiatrist is rewarded by a remarkable increase in the patient's quality of life. This relatively high expenditure of time should be devoted more often than is usually the case up to now. Severe symptoms and complex problems should be regarded as a great challenge. Facing this challenge will be profitable for the patient as well as for the therapist. Details of the multidimensional setting deserve being discussed, especially with regard to its feasibility in different countries.

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