tive and negative, disorganization, difficult contact) and non-specific for schizophrenia (depresion, anxiety and tension, excitement). One could conclude that factorial structure detected in empirical analysis of syndromes created by different diagnostic criteria and described by different diagnostic instruments may be different both in number and contents of the final factors. This problem should be carefully analysed as up to date there is no generally accepted valid definition of schizophrenia.

CLINICAL ASSESSMENT OF SCHIZOPHRENIC SYNDROMES (CASS) — EVALUATION OF THE NEW DIAGNOSTIC TOOL

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CASS was constructed as an auxiliary instrument for diagnosing, describing, and rating schizophrenic syndromes. It consists of four parts: (1) CASS-D: diagnostic questionnaire facilitating the diagnosis of schizophrenia according to DSM-IV and ICD-10 criteria; (2) CASS-G: scale for global rating of severity of an observed syndrome; (3) CASS-D: 13 scales for rating selected clinical dimensions of the syndrome; (4) CASS-S: 31 scales for more detailed rating of selected symptoms of the syndrome. For constructing the CASS scales dimensions (groups of symptoms sharing hypothetically common psychopathological meaning) and symptoms were selected which are either specific (e.g. ego distortion, thought disorganization or deficit symptoms) or non-specific (e.g. mood or drive changes) but important for clinical assessment of schizophrenia. All ratings are made on analogously defined 4-point (0–3) oridinal scales. Two studies were conducted to evaluate basic psychometric properties of the CASS. In the first one, each of 2 teams of 3 psychiatrists rated a group of 24–25 patients with clinical diagnosis of schizophrenia. Ratings were made by each clinician's independently after common assessment during clinical conference. In the second study, 194 consecutively admitted patients were assessed by their psychiatrist twice, at the time of admission and discharge. Results allow to state good inter-rater reliability of sum scores of the CASS scales (Kendall's W for: CASS-G > 0.86, CASS-D > 87, CASS-S > 92), and good reliability measured as internal consistency (Cronbach's alpha for CASS-D = 0.83; for CASS-S = 0.91) of its composite scales. Moderate (CASS-G: $0.37 < tau^b < 0.46$; $0.46 < r < 0.55$) or high (CASS-D, CASS-S: $0.60 < tau^b < 0.72$; $0.77 < r < 0.89$) correlations of CASS with BPRS, PANSS and SANS/SAPS as internationally approved standard tools seem to confirm its concurrent validity. Interesting and meaningful results of analysis of frequency, intensity, and specifity (for schizophrenia) of dimensions and symptoms analysed as well as of sum scores of the CASS scales may confirm external (content) validity of the instrument. Conclusions from principal components analysis of underlying structure of the schizophrenic syndromes described by CASS-D and CASS-S increase confidence in their internal (theoretical) validity also. Meaningful variability and range of indices of improvement between admission and discharge could be interpreted as an evidence of the CASS sensivity to change.

ELECTRICAL BRAIN ACTIVITY REFLECTING SEMANTIC MEMORY ACCESS IN NORMAL VOLUNTEERS AND SCHIZOPHRENIC PATIENTS: EVIDENCE FROM INDIRECT SEMANTIC PRIMING

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Event-related potentials (ERPs) are a powerful tool for monitoring the working brain on-line. The goal of this study was to investigate the time course and the topography of ERPs during the performance of a semantic priming paradigm in normal subjects and schizophrenic patients. ERPs were collected with 64 electrodes while were presented with a prime and a subsequent string of characters as the target (50% words, 50% non-words). Primes and target-words were either directly related (hen-egg), indirectly related (lemon-sweet) or not related (sofa-wing). As in our previous studies, semantic relatednes had a systematic influence on N400 amplitude and latency. Moreover, the N400 component was different in patients and controls. In particular, the indirect condition distinguished patients and controls most clearly. A left frontal activation beginning about 300 ms post stimulus onset was found in both groups: Directly related target words produced more left frontal activation whereas indirectly related words produced more right frontal activation. This frontal effect confirms findings of other functional neuroimaging studies (PET, fMRI) and may reflect semantic memory activation. Schizophrenic patients showed more right frontal activation than controls. This finding is in line with larger indirect semantic priming effects in thought disordered schizophrenic patients.

SINGLE AND MULTIPLE DOSE PHARMACOKINETICS OF ZIPRASIDONE IN HEALTHY MALES

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The pharmacokinetics of ziprasidone, an antipsychotic agent with combined antagonism at $5HT_{2A}$ and D_2 receptors, were investigated in 30 healthy male subjects using a randomized, placebo-controlled study design. Once-daily (days 1 and 18) and twice-daily doses (days 4 to 17) of placebo, and 5, 20, 40, and 60 mg ziprasidone were administered in the fed state to five groups of six subjects. The 40 and 60 mg ziprasidone groups received 20 mg on day 1 and were titrated to the final dose by day 10. Mean pharmacokinetic parameters (day 1/day 18) were:

Dose (mg)	AUC (0–12) (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
5	74/ 110	12/ 15	5.0/5.2	3.2/ 4.0
20	176/ 259	27/ 45	4.8/3.8	4.8/ 4.8
20 → 40	315/ 658	60/119	3.8/3.7	4.0/ 8.8
20 → 60	215/1028	34/139	4.0/4.7	4.3/10.0

Steady-state conditions were attained after one day of dosing. Mean C_{max} and AUC (0–12) increased with increasing dose and mean accumulation ratios for the 5 and 20 mg dose levels were 1.49 and 1.48 respectively. Accumulation ratios were not calculated for the higher doses because of the titration. Longer steady-state half-lives at the higher doses were associated with increased body load of drug leading to the appearance of an additional dispositional phase. The steady-state peak to trough concentration ratios generally ranged from 2 to 5.

MULTIPLE-DOSE PHARMACOKINETICS OF 'SEROQUEL" (ICI 204,636) IN SCHIZOPHRENIC MEN AND WOMEN

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'Seroquel' (ICI 204,636) is a dibenzothiazepine derivative currently in Phase III clinical development as an antipsychotic agent. The objectives of this study were to investigate the multiple-dose pharmacokinetics and safety of ICI 204,636 in schizophrenic men and women. Twenty-eight patients (13 men and 15 women) aged 21 to 42 years with a clinical diagnosis meeting the DSM-III-R criteria for schizophrenia entered this trial. After a 2-day washout period, patients were

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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