EVIDENCE FOR SIMILAR DEVELOPMENTAL PRECURSORS OF CHRONIC AFFECTIVE ILLNESS AND SCHIZOPHRENIA IN A GENERAL POPULATION BIRTH COHORT

J. van Os, P. Jones, G. Lewis, M. Wadsworth, R. Murray. *Institute of Psychiatry, De Crespigny Park, London SE5 8AF*

Is childhood developmental deviance preceding schizophrenia diagnosis-specific? We examined associations between childhood developmental data and both chronic affective disorder and schizophrenia, in a prospectively studied national British birth cohort of 5262 individuals born in the week March 3–9th 1946. 75 cases (prevalence: 2.3%) with chronic, severe affective disorder (CAD), and 30 cases with schizophrenia or schizoaffective disorder (SZ) were identified. Significant interaction with gender was present in the associations between CAD and developmental risk factors. Attainment of motor milestones was later in female CAD cases (OR women = 1.5; 95% CI: 1.1–2.2), followed by greater risk of speech defects between the ages of 6 and 15 years (OR women = 3.6; 1.8–7.5). At ages 8, 11 and 15 years, educational test scores differentiated between CAD cases and controls, especially in girls. At ages 13 and 15, CAD cases were more likely to be rated "persistently sad and gloomy" by their teachers (OR's 2.7 & 2.5; $p < 0.05$). Similar, possibly stronger, associations were demonstrated for SZ cases. The results suggest that early social, cognitive and motor deficits are either the early manifestation of a unitary syndrome, or the manifestation of a common predisposition to severe mental illness.

SEASON AND PLACE OF BIRTH IN A SAMPLE OF 22361 PATIENTS WITH A DIAGNOSIS OF SCHIZOPHRENIA

J.J.van Os, N. Takei, F. Navarro Mateu, R.M. Murray. *Section of Social Psychiatry and Psychiatric Epidemiology, University of Limburg, PO BOX 616, 6200 MD Maastricht, The Netherlands*

Objectives: Many infectious diseases are more prevalent in the autumn and winter months, and are transmitted more easily in densely populated areas. Therefore, the finding that the excess of winter birth among patients with schizophrenia is especially marked for those born in urban areas, would support the hypothesis that early exposure to infectious agents increases the risk for later schizophrenia. *Methods:* We examined associations between season of birth and population density of place of birth in a national sample of 22361 patients with schizophrenia, who were discharged from psychiatric hospitals and units in the Netherlands from 1970 to 1993. *Results:* Significant effect modification by gender was apparent, in that in women, but not in men, winter birth was associated with population density of the area of birth (OR women: 1.12, 95% CI: 1.00–1.25, P = 0.05). *Conclusions:* These data are consistent with studies linking prenatal exposure to influenza and later schizophrenia in women.

A PROPOS DE 3 CAS DE SCHIZOPHRENES RESISTANTS TRAITES PAR CLOZAPINE ET FLUOXETINE: DE L'INTERET DES DOSAGES PLASMATIQUES ET GLOBULAIRES ASSOCIES AU SUIVI CLINIQUE

A. Viala [2], N. Aymard [1,3], C. Boyer [3], S. Rampa [2], S.F. TriboletCaroli [2]. [1] *Unité de Pharmacologie, Centre Hospitalier Sainte Anne-1, rue Cabanis 75014, Paris;* [2] *Unité Médico Psychologique du 14ème arrondissement ouest, Centre Hospitalier Sainte Anne-1, rue Cabanis 75014, Paris;* [3] *Laboratoire de Pharmacologie, Université René Descartes, Paris, France*

La Clozapine (Cloza) est un neuroleptique atypique utilisé pour traiter les schizophrènes résistants aux traitements conventionnels. Lors de l'évolution sous traitement, on peut constater chez les psychotiques l'apparition d'un syndrome dépressif secondaire que nous avons été amenés à traiter par la Fluoxétine (Flu), inhibiteur spécifique de la recapture de la sérotonine (SSRI) que nous pouvons doser; A l'occasion des bilans biologiques indispensables dans le cadre de la prescription de la Cloza (une fois par semaine pendant les 18 premières semaines puis au moins une fois par mois par la suite) nous avons pratiquè: des dosages plasmatiques (P) et globulaires (G) de Cloza et de son dérivé, la desmetylclozapine (Descloza) ainsi que de Flu et de son dérivé déméthylé (NFlu) (les concentrations globulaires sont représentatives des fractions libres des médicaments), des entretiens complétés par des échelles cliniques (BPRS – échelle de dépression psychotique et de qualité de vie (Heinrichs, Hanlon et Carpenter) et des EEG à intervalle régulier.

A propos de 3 cas de patients schizophrènes résistants (2 H — 1 F, 25, 33 et 43 ans), selon les critères du DSM III R, traités d'abord par Cloza seule puis, secondairement déprimés, par Cloza et Flu (20 mg/jour) associés, nous avons pu mettre en évidence: i. une dose majeure efficace de Cloza, fixe pour chacun d'entre eux (de 250 à 700 mg/j), ii. une concentration utile pour la plus faible posologie avec le minimum d'effets secondaires (200 à 700 et 100 à 400 ng/ml pour la P et G Cloza avec des rapports P. Cloza/Descloza = 1.86 ± 0.56 — G Cloza/Descloza = 1.53 ± 0.56), iii. un cas de diminution des polynucléaires neutrophiles à forte concentration de Cloza nécessitant une adaptation thérapeutique à la baisse, iiii. une mauvaise compliance au traitement (1 patient sur 3) en repérant notamment les interruptions de celui-ci à l'occasion du week end, iiiii. les modifications EEG et iiiiii. une augmentation significative des concentrations P. de Cloza et Descloza à partir du moment où le steady state de Flu est atteint. Nous avons constaté une diminution concernant d'abord les symptomes d'inhibition puis la production psychotique, avec amélioration de qualité de vie ayant permis une autonomie en dehors du suivi d'hospitalisation, avec amélioration en premier lieu des contacts et des relations interpersonnelles.

COMPONENTS OF THE SCHIZOPHRENIC SYNDROME — INFLUENCE OF DIAGNOSTIC CRITERIA AND INSTRUMENTS

J. Wciórka. *Institute of Psychiatry and Neurology, Department of Psychiatry I, Al. Sobieskiego 1/9, 02-927 Warsaw, Poland*

Current discussions on the number and contents of factors creating a typical schizophrenic syndrome are not conclusive. Opinions and research results differ according to many variables. Some authors accentuate the problems connected with influence of methodological choices on research findings obtained. The aim of this study was to analyse to what degree (1) diagnostic criteria used for separating the investigated group of schizophrenic patients and (2) instruments used to describe the psychopathological contents of the schizophrenic syndrome observed may influence the results of a statistical procedure applicated to study the underlying structure of the syndrome. From the population of 194 patients consecutively admitted to psychiatric department two groups was separated fulfilling the ICD-10 (N = 78) or DSM-IV (N = 68) criteria of schizophrenia. The diagnosis was satisfactory concordant (kappa = 0.85). Mental state of all patients was rated by the 30-items PANSS and 9-items (only global ratings) SANS/SAPS scales. Principal components analysis with identical method of factor extraction and rotation was then performed for both criteria and both instruments deriving groups. SANS/SAPS scales replicated the popular three-factors solution (interpreted as positive, negative, and disorganization), but only in the ICD-10-schizophrenia group. In the DSM-IV-schizophrenia group two-factors solution resulted (interpreted as positive and negative). PANSS analysis allowed to detect eight- (for DSM-IV) or seven-factors (for ICD-10) solutions. The contents of factors were rather similar, with some differences both among the factors which could be treated as specific (posi-

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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

J. Wciórka. *Institute of Psychiatry and Neurology, Department of Psychiatry I, Al. Sobieskiego 1/9, 02-927 Warsaw, Poland*

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

M. Weisbrod, M. Kiefer, I. Kern, S. Maier, M. Spitzer.

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

K.D. Wilner [1], R.A. Hansen [1], A.C. Johnson [1], J.J. Miceli [1], G. Apseloff [2], N. Gerber [2]. [1] *Department of Clinical Research, Pfizer Central Research, Groton, CT 06340, USA;* [2] *Department of Pharmacology, Ohio State University, Columbus, OH 43210-1239, USA*

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

J.Y.W. Wong, B.J. Ewing, L.F. Fabre, P.T. Thyrum, C. Yeh. *Zeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE USA*

'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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