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AMISULPRIDE IN PRIMARY NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Several studies have demonstrated the efficacy of amisulpride in acute patients, presenting predominant positive symptoms. In chronic schizophrenic patients with primary negative symptoms, amisulpride, is the only antipsychotic having consistently demonstrated efficacy. In order to determine the minimum effective dose, 50 mg/d (ami 50), 100 mg/d (ami 100), and placebo (pl) were compared in a 3-month double-blind, randomized, multicentres study. Residual schizophrenic patients (DSM III-R criteria) were carefully selected for having primary negative symptoms. After one month of washout placebo period, 242 patients were randomized (pl: 83; ami 50: 84; ami 100: 75). All the three groups were comparable at baseline. Only 60% (50) of placebo-treated patients ended the study (83% and 80% in ami 50 and 100 respectively). Both amisulpride groups showed statistically significant differences compared with placebo group: mean (std) SANS total score change pl: 13.4 (23.2); ami 50: 24.8 (19.2); ami 100: 25.4 (19.1) ($p = 0.0002$). All other efficacy criteria showed also significant improvement in ami groups compared to placebo (SANS factors, BPRS, SAPS, and MADRS). Safety was comparable in the three groups, and psychiatric disorders, as well as central and peripheral nervous system adverse events, were the most frequently adverse events reported. Simpson Angus scores were low at baseline and endpoint and change was not different between placebo and the two amisulpride groups.

Conclusion: amisulpride 50 and 100 mg/d showed superior efficacy and similar safety compared with placebo in the challenging treatment of primary negative symptoms in schizophrenic patients.

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ZUCLOPENTHIXOL ACETATE IN PATIENTS WITH ACUTE PSYCHOSIS. AN OPEN MULTICENTRE STUDY

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Objectives: to evaluate the clinical effect and tolerance of zuclopenthixol acetate (ZPT-A) in the treatment of acute psychosis

Methods: the trial was conducted as an open, clinical multicentre study in 30 departments of psychiatry in Spain. Patients included were diagnosed according to ICD-9 as suffering acute psychosis, mania or an exacerbation of a chronic psychosis, needing hospitalisation and pharmacological treatment. Patients were not selected if they had received oral neuroleptics within the last 6 hours, depot neuroleptics within the previous 2 weeks, were suffering from a serious somatic disease or known organic cerebral disease or were pregnant women. On entry, patients received an injection of ZPT-A, adjusted to individual needs (50–150 mg). If necessary, another injection (50–100 mg) was given after 72 hours. No other neuroleptics were allowed. The severity of illness was rated according to the BPRS and CGI scales. UKU rating scale was used to evaluate side effects. Controls were performed on entry and subsequently daily for the following 6 days.

Results: 277 patients were included in the study (167 men, 110 women, average age 32.3 and 37.2 years, respectively). The average dose of ZPT-A administered was 92.9 mg in the first injection and 97 mg in the second. BPRS mean score at entry was 30, and at day 6 was 12 ($p < 0.001$). CGI score was 4.4 at entry and 2.57 after the 6 days of treatment ($p < 0.001$). The side effects were mild in most of the patients, with little interference on their functioning.

Conclusion: zuclopenthixol acetate given as intramuscular injection is useful and safe in the treatment of acute psychosis.

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^{3}H-SPIPERONE BINDS WITH HIGH AFFINITY TO A NON-DOMPAMINERGIC SITE ON HUMAN B-LYMPHOCYTES, EBV-TRANSFORMED LYMPHOBLASTS AND MACROPHAGES

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The findings of LeFur et al. (1983) and Bondy et al. (1985) that the binding to native lymphocytes is elevated in schizophrenia and possibly in affective psychosis (Fartacek et al., 1997) stimulated the search for the pharmacological basis of this binding site. As blood-derived lymphocytes consist of several subpopulations, this study investigates the binding of ^{3}H-spiperone using different white blood cells and artificial cells of human blood cell origin.

B-lymphocytes and macrophages were characterised by a saturable (K_D 0.1 nM, B_{max} 0.5–2.5 $\times$ 10^{-15} mol/10^6 cells) and a nonsaturable binding above 1 nM ^{3}H-spiperone. EBV-transformed lymphoblasts of B-cell origin had nearly the same affinity for spiperone but the number of binding sites was about three times higher. Membrane preparations of these lymphoblasts exhibited a similar binding profile as native cells.

T-cells (which represent up to 70% of native lymphocyte suspensions), granulocytes and T-cell derived MOLT-3 cells did only present a nonsaturable binding which increased threefold after immunological stimulation. The pharmacological profile of the high-affinity ^{3}H-spiperone binding site was clearly different from dopaminergic D_2 and D_4, serotonergic 5-HT_2, histaminergic H_1, noradrenergic α_1 and α_2 and cholinergic M_1 receptors.

We conclude that circadian and immunological factors might contribute to a different composition of cellular subtypes of white blood cells, which in turn leads to a different apparent density of spiperone binding sites in psychiatric patients and controls, due to variable amounts of binding to saturable (e.g., B-cells) and unsaturable (e.g., T-cells) binding sites. Homogenous EBV-transformed cell lines are recommended for further pharmacological investigations of the spiperone binding site.

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SUBJECTIVE EXPERIENCE OF PATIENTS ON OLANZAPINE IN COMPARISON TO OTHER ANTIPSYCHOTICS

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Background: Based on indications that clozapine is better tolerated and liked by patients, the novel antipsychotic (AP) olanzapine may also have similar effects based on subjective experience. Subjective experience on AP's can be seen as the sum of all subjective reactions to AP's, including psychic, somatic, and social functioning. A positive subjective experience may result in an improved compliance to medication. The objective of this study is to explore each component of the subjective experience during olanzapine treatment in comparison to other AP's.

Methods: Thirty eight in/outpatients with diagnosed DSM-IV schizophrenia, schizophreniform or schizoaffective disorder who had received at least 4 weeks of typical or atypical AP therapy, received olanzapine 5–20 mg/day for 26 weeks in an open-label prospective naturalistic study. Subjective Well-being (SW on Neuroleptics scale, SWN), improvement on overall symptomatology

https://doi.org/10.1016/S0924-9338(99)80635-X Published online by Cambridge University Press

(Brief Psychiatric Rating Scale, BPRS), Global Assessment of Functioning (GAF) current overall functioning, Patient Evaluation of Medication (PEM) and safety (Clinical Global Impression of side effects (CGI-se) and Patient Global Impression of side effects (PGI-se) were measured at baseline and after 6, 14 and 26 weeks. Statistical methods used are t-tests for related samples. Percentage changes are expressed as relative to the maximum change possible.

Results: As this study is in progress preliminary results are reported over 19 patients, and are only available for change at week 14 compared to baseline. Mean improvements turned out to be 20.8% in SWN ($p = 0.012$), 24.8% in BPRS ($p = 0.002$), 5.4% in GAF ($p = 0.004$) and 58.8% in PEM ($p = 0.002$). Regarding side-effects, the mean improvements were 62.2% in CGI-se ($p = 0.009$) and 38.7% in PGI-se ($p = 0.042$).

Conclusions: Patients rated their subjective experience with olanzapine significantly superior to their previous AP. Their overall well-being and symptomatology improved significantly as well as their current overall functioning. Side effects were significantly better tolerated. Patients indicated to prefer olanzapine treatment over their previous AP.

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THE USE OF THE ATYPICAL ANTIPSYCHOTIC OLANZAPINE IN SCHIZOPHRENIA

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During the past decades, efforts have been undertaken to develop antipsychotics which combine an antipsychotic effect and a profile of low extrapyramidal side effects. Two major classes of atypical antipsychotic compounds have become available, the 5-HT/DA antagonists with strong $5\text{-}HT_{2a}$ relative to DA_2 receptor blocking properties of which risperidone is the main representative (Verhoeven et al., 1997) and the group of clozapine related drugs that affect various DA and 5-HT subreceptor systems such as olanzapine and sertindole.

In the present study the effect of olanzapine in a flexible dose from 5 to 20 mg daily was investigated on the schizophrenic symptom profile and 5-HT plasmaparameters. In an open, prospective study lasting 14 weeks, the efficacy of olanzapine on positive and negative symptoms was assessed by means of the PANSS and the CGI including a total of 20 patients suffering from either an acute type of schizophrenia or an acute episode, a relapse after symptom free interval or an exacerbation of chronic illness.

Preliminary analyses revealed a reduction of both positive and negative symptoms in a majority of the patients included, albeit the effect seemed to be more pronounced on negative symptoms. Major side effects comprised weight gain and fatigue, not necessitating premature discontinuation; extrapyramidal side effects were not observed.

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SERTINDOLE IN THE TREATMENT OF SCHIZOPHRENIA

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Subjects: 9 patients who fulfilled the DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder and gave informed consent. Mean age (± SD) was 28.8 (± 5.4) years.

Methods: We openly treated the patients with sertindole (SRT). No other antipsychotic drug was used. The average dose of SRT was 17.1 (± 5.1) mg/day. Mean length of treatment was 3.7 (± 4.3) months. Two patients were treated with SRT alone, and 7 patients were treated with SRT in combination with benzodiazepines (N = 5), carbamazepine (N = 2), valproate (N = 1), lithium (N = 1), gabapentin (N = 1), and paroxetine (N = 1). The t-test was used for comparison between assessment on admission and at the last evaluation.

Results: On admission, the patients received the following mean (± SD) scores: CGI: 6.2 (± 0.4), BPRS: 34.7 (± 15.8), SAPS: 43.1 (± 30.3), SANS: 46.6 (± 22.0), GAF: 26.0 (± 7.4). At the last visit, patients had a significant mean improvement on the CGI (4.8 ± 1.6; $p = 0.017$), and the GAF (37.8 ± 11.3). Improvement on the BPRS was marginally significant (19.7 ± 17.9; $p = 0.078$). There was a numeric (but not statistically significant) improvement on the SAPS and the SANS. We observed no acute dystonic reaction. Rigidity, akathisia and other specific parkinsonian signs were absent or minimal. Three patients had a significant akinesia. However, the treatment with SRT improved this sign in all of them, suggesting that akinesia was a primary negative symptom and not a drug side effects in such patients. One patient treated with SRT (20 mg/day) in association with lithium (900 mg/day) showed a severe, diffuse, high frequency, irregular tremor which did not improve after withdrawal of lithium and SRT. Furthermore, we observed nasal congestion (N = 2), somnolence (N = 4), absence of ejaculation and reduced libido (N = 3), ventricular premature complexes (N = 1), and weight gain (N = 5) (Kg: 12, 8, 4, 9, 5).

Discussion: In this sample, SRT was effective against both the positive and negative symptoms of schizophrenia spectrum disorders. Neurological side effects were absent or minimal. Absence of ejaculation and weight gain were the most serious treatment-emergent adverse events.

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THE CARDIOVASCULAR SAFETY PROFILE OF SERTINDOLE. PRELIMINARY DATA

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Objective: Cardiovascular safety of Sertindole, an atypical antipsychotic patented by H. Lundbeck, has critically been discussed because in some patients Sertindole may induce a slight prolongation (about 5%) of the QT-interval in the ECG. A similar QT-prolongation is well known from class IA/III antiarrhythmic drugs. Excessive prolongation of the QT-interval especially in combination with pre-existing certain heart diseases, electrolyte disturbances (K, Mg) and bradycardia increases the likelihood of the development of ventricular tachycardia (Torsades de pointes). However, bradycardia is not known to be part of the clinical profile of Sertindole. In addition the drug binds with relatively high affinity to alpha-1-adrenergic receptors. This may exert an inhibitory effect on some arrhythmogenic mechanisms. Nevertheless, another important (and unfortunately often overlooked) aspect to assess

https://doi.org/10.1016/S0924-9338(99)80635-X Published online by Cambridge University Press