pine was superior to haloperidol for key symptom domains and parkinsonian adverse events. Implications of these data for the therapeutics of this severely ill subgroup are discussed.

101. RELAPSE PREVENTION WITH OLANZAPINE

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The objective of this study was to assess the efficacy of olanzapine, compared with placebo in preventing psychotic relapse in stable, minimally symptomatic patients with schizophrenia.

Patients who had been outpatients, minimally symptomatic, and stable for at least 6 weeks underwent prospective conversion to olanzapine over the course of 6 weeks followed by an 8-week observation period to prospectively confirm stability. Patients who were stable on a fixed dose of olanzapine monotherapy prior to enrollment entered the 8-week observation phase to confirm stabilization. Following 6 to 14 weeks of observation, 224 patients were randomized to continued oral olanzapine, 10–20 mg/day and 102 patients were randomized to placebo. Patients were examined in person at least every 2 weeks and telephone contact was required if patients were not examined in person at least weekly. Statistical methods allowing sequential monitoring of relapse rates were employed to protect against continuing an ineffective treatment.

Based on robust superiority of olanzapine, the study was terminated early. By Kaplan-Meier analysis, the 6-month cumulative relapse rate for olanzapine was 6% and for placebo was 55%. The difference between treatment groups in the time to relapse curves was significant (p < 0.001). Additional efficacy and safety results will be discussed along with the monitoring techniques.

102. KINETICS AND SAFETY OF A NOVEL RISPERIDONE DEPOT FORMULATION

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The bioavailability of a new intramuscular depot formulation and of oral doses of risperidone was assessed in patients with schizophrenia. Three groups of stable patients with schizophrenia received oral doses of risperidone (2, 4, or 6 mg/day) during weeks 1–3 and oral risperidone at half those doses during weeks 4–5. During weeks 2–10, the three groups received depot doses of risperidone (25, 50, or 75 mg, respectively) every 2 weeks (5 injections). Plasma concentrations of unchanged risperidone and of the active moiety (risperidone + 9-hydroxyrisperidone) were determined: Efficacy, adverse events, vital signs, and the injection site were evaluated regularly. Total daily exposure to the active moiety was equivalent after oral and depot dosing, i.e., the 90% confidence intervals for the mean steady state AUC and Cav ratio (depot vs. oral) were all within the bioequivalence range of 80% to 120%. Peak plasma concentrations were significantly lower (25% to 32%) after depot than oral dosing. The most frequent adverse events were either influenza-like symptoms or of a psychiatric nature. No consistent, clinically relevant changes in vital signs, ECG, or laboratory test results were observed. Only minor discomfort at the injection site was noted in a few patients. Patients remained symptomatically stable when treatment was changed from an oral to a depot regimen. Bioequivalence of oral and IM depot dosing of risperidone was demonstrated. Moreover, IM depot dosing was as well tolerated and efficacious as oral dosing.

103. THE IMPLICATIONS OF ANTIPSYCHOTIC TREATMENT PATTERNS ON HEALTH OUTCOMES IN SCHIZOPHRENIA

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We assessed the impact of continuous therapy (CT), intermittent therapy (IT), or low-exposure therapy (LT) on quality of life in the usual care setting for patients with schizophrenia. Data on prescribed and dispensed medications, assessments of quality of life, symptoms, and hospitalizations from a one-year, naturalistic, randomized clinical trial were analyzed. Of 546 patients who completed the study, 159 were treated with CT (≥90% of study days on drug), 248 with IT (<90% and ≥50% days on drug, and intermittent use), and 139 with LT (≤50% days on drug). Patients were further classified as receiving monotherapy or polytherapy. SF-36 Mental Component Scores (MCS) and risk of relapse were compared for each group using regression models. Relative to LT, patients treated with CT or IT had better MCS at one year (both p ≤ 0.01). Risk of relapse was lower for patients receiving CT (OR = 0.33, p < 0.01) and IT (OR = 0.78, p = 0.43), relative to LT. There were no differences in MCS for patients treated with monotherapy or polytherapy, however, patients receiving monotherapy had a 69% lower risk of relapse (p < 0.01). These results suggest a high proportion of patients in usual care do not receive optimal maintenance therapy following acute relapse. Continuous therapy was associated with better quality of life and relapse prevention than other patterns of treatment, and monotherapy reduced patients’ risk of relapse.

104. RISPERIDONE VS HALOPERIDOL FOR RELAPSE PREVENTION IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: A LONG-TERM DOUBLE-BLIND COMPARISON

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A multicenter, randomized, double-blind comparison of risperidone (RIS) and haloperidol (HAL) in stable outpatient schizophrenics and patients with schizoaffective disorder was conducted to compare the time to relapse. Patients continued double-blind treatment until the last patient had completed 1 year. Assessments were made weekly for the first 4 weeks and at 4-week intervals thereafter. Scales used to assess efficacy included the total score on PANSS and all PANSS subscale scores. Safety evaluations included ESRS and clinical laboratory tests, including weight gain. Of 365 treated patients in the trial, 41 (23.2%) in the RIS and 65 (34.6%) in the HAL groups relapsed by the end of the first year (OR = 0.33, p < 0.01). During the entire trial, 45 (25.4%) patients on RIS and 75 (39.9%) patients on HAL relapsed (p = .002). Patients in the RIS group experienced only a modest degree of weight gain (5.0 lbs at endpoint), a low rate of TD (0.6%), and a low rate of EPS. This study provides evidence for the long-term effectiveness of RIS and corroborates earlier pivotal trials in which RIS was found to be significantly
superior to HAL against both positive and negative symptoms of schizophrenia. Previous short-term trials have shown RIS to be statistically superior to HAL in the control of positive and negative symptoms. This trial confirms the superior efficacy of RIS over HAL in long-term treatment. Patients treated with RIS also experienced a desirable safety profile in long-term treatment.

105. RISPERIDONE VS. OLANZAPINE IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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We report the first large controlled trial comparing risperidone (RIS) and olanzapine (OLA) at doses most frequently used in clinical practice. 407 adults at 41 sites received flexible doses of RIS (2–6 mg/day) or OLA (5–20 mg/day) for 8 weeks. Assessments included PANSS, ESRS, vital signs, and blood testing. Statistical testing was two-tailed. Two sites were excluded due to data quality concerns, leaving 377 patients for analysis. Data quality was verified by audit of every patient file and site. Mean modal doses were 4.8 mg/day (RIS) and 12.4 mg/day (OLA). Age differences at baseline (p < 0.05) were corrected in analysis of PANSS and ESRS. Both drugs were associated with significant and similar improvements in symptoms (total PANSS). However, among patients completing 8 weeks, there was a statistically significant advantage for RIS on PANSS subscales for anxiety/depression (p < 0.02) and positive symptoms (p < 0.05). A greater proportion of RIS patients had positive symptom improvement (reaching significance at the 40% or more improvement level, p < 0.03). There was no statistically significant difference in adverse events related to extrapyramidal symptoms or on the magnitude of improvement in extrapyramidal symptoms (total ESRS score). OLA patients had significantly greater increases in mean body weight and BMI. Patients treated with RIS or OLA had significant clinical improvement from baseline. Both drugs were generally well tolerated. This study suggests efficacy advantages for RIS, particularly with regard to anxiety/depression and positive symptoms. With the exception of substantial weight gain among OLA patients, this study finds similar overall tolerability profiles.

106. INDIVIDUAL COGNITIVE PROFILE ANALYSIS IN SCHIZOPHRENIA: EVIDENCE FROM A NEW SAMPLE

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The question of whether schizophrenia is a unitary or heterogeneous disorder remains a subject of debate and controversy that is central to our understanding of the illness. Based on the strategy developed by Seidman et al. (1993), Kremen et al. (1999) examined neuropsychological heterogeneity in schizophrenia using individual-case clinical neuropsychological descriptions as a starting point for group comparisons. We refer to this as a hybrid individual/group approach because groups are constructed on the basis of “blind” ratings of individuals. For each subject, we made quantitative (severity) ratings and qualitative (profile type) ratings. Profile types were based primarily on prototypes from the clinical literature in neuropsychology. In the previous study these types included: within normal limits, left temporal/verbal memory, frontal abstraction, widespread/diffuse, and other. In the previous work, which was carried out with chronic schizophrenia patients and normal controls, the subgroups differed in terms of both severity and profile shapes (group × function interactions). To further examine the usefulness of this approach for studying heterogeneity in schizophrenia, we are now applying this method to an independent sample of first-episode schizophrenia patients (n = 58), chronic state hospital schizophrenia inpatients (n = 74), and normal controls (n = 74) collected by Hoff et al. (1992, 1998). Test scores are adjusted for age, sex; and parental SES. We will compare the similarities and differences in the groupings that emerge from this new sample to those of the previous sample. We will also present data on between-group differences in profile shape and in demographic and clinical characteristics.

107. INDIVIDUAL COGNITIVE PROFILES IN SCHIZOPHRENIA: HETEROGENEITY OR CHANGE OVER TIME?

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Whether schizophrenia is a unitary or heterogeneous disorder continues to be debated. Based on the strategy developed by Seidman et al. (1993), we examined neuropsychological heterogeneity in schizophrenia using individual-case clinical neuropsychological descriptions as a starting point for group comparisons. With this hybrid individual/group approach, we blindly rated neuropsychological profiles of 74 schizophrenia patients and 91 normal controls based primarily on prototypes from the clinical literature in neuropsychology. Test scores were adjusted for age, sex, and parental education. Patients were classified as having the following profile types: within normal limits (n = 17), left temporal/verbal memory (n = 6), frontal abstraction (n = 34), widespread/diffuse (n = 10), and other (n = 7). These groups were each significantly different from one another and from controls in terms of both severity (main effects) and profile shapes (group × function interactions). We found quantitative differences in that groups with greater overall cognitive impairment had longer duration of illness, even when age of onset was the same. However, the group × function interactions indicate qualitative differences; for example, the left temporal/verbal memory group had worse verbal memory but better performance on abstraction/executive and other functions than the frontal abstraction group. This double dissociation of function cannot be explained on the basis of generalized deficit. Our approach appears to reveal patterns not easily seen with other methods of examining heterogeneity in schizophrenia, but additional research (e.g., brain imaging and longitudinal studies) will be needed to determine whether the different neuropsychological profiles reflect true group differences or within-person change over time.