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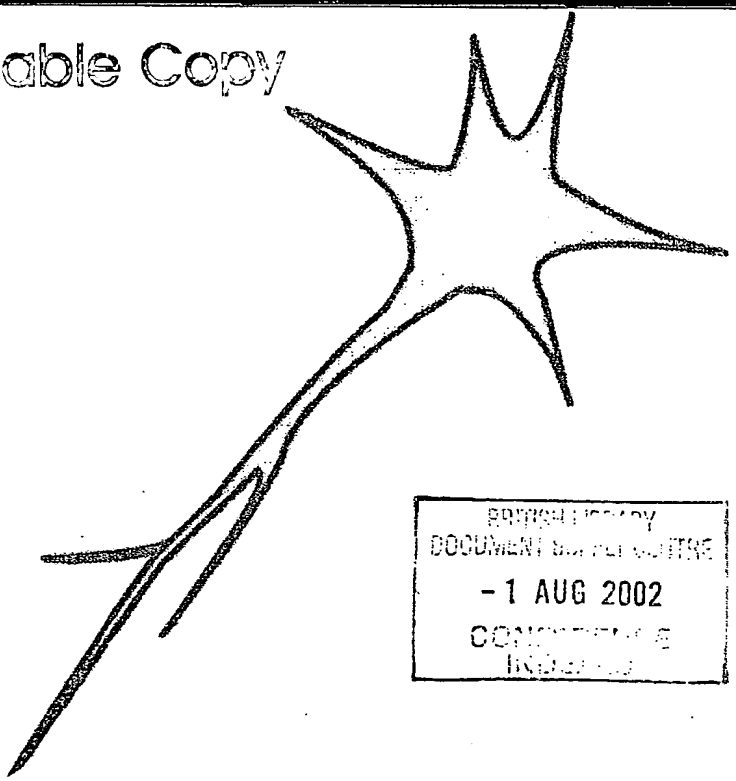

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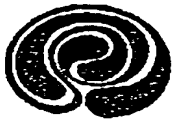

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dose reduction was allowed to aripiprazole 20 mg and haloperidol 7 mg. Efficacy evaluations included PANSS and MADRS scores.

Results: A significantly greater proportion of patients treated with aripiprazole demonstrated response and remained on treatment at weeks 8, 26, and 52 compared to haloperidol (Week 52: 40% vs 27%, $p<0.001$). Aripiprazole produced statistically significant improvements in the PANSS Negative Subscale Score at weeks 26 and 52 (both $p<0.03$). Aripiprazole also demonstrated significant improvement from baseline in depressive symptoms as shown in the MADRS at weeks 8, 26, and 52, compared to haloperidol (all $p<0.03$). The discontinuation rate due to an adverse event was significantly lower in the aripiprazole group than in the haloperidol group ($p<0.001$). The overall incidence of EPS-related adverse events was significantly lower with aripiprazole than with haloperidol ($p< 0.001$). Both treatments resulted in comparable weight gain. There was no significant difference in QT_c interval between both groups.

Conclusion: Aripiprazole may represent the next-generation antipsychotic leading to increased compliance in schizophrenia due to significantly greater improvements in negative and depressive symptoms, and a superior safety and tolerability profile compared to haloperidol.

P.4.E.033 ARIPIPRAZOLE VS. PLACEBO IN THE TREATMENT OF CHRONIC SCHIZOPHRENIA

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Objective: To assess relapse prevention with aripiprazole compared to placebo over 26 weeks in patients with chronic but stable schizophrenia.

Methods: A multicenter, randomized, double-blind, placebo-controlled study was conducted in 310 patients with chronic schizophrenia considered stable (no significant improvement or worsening in last 3 months and baseline PANSS=82) randomized to aripiprazole 15 mg/day or placebo. Efficacy measures included time-to-relapse, number of relapses and PANSS total score.

Results: Compared to placebo, treatment with aripiprazole was shown to be effective in increasing time-to-relapse, and resulted in significantly fewer patients relapsing at endpoint versus placebo (34% vs. 57%, respectively). Aripiprazole produced significantly greater improvement in PANSS total score and PANSS positive subscale score, compared to placebo. Patients on aripiprazole showed continuing stability on the PANSS negative subscale score. Aripiprazole was generally well tolerated with an adverse event profile comparable to placebo. No clinically significant changes occurred in SAS, AIMS, and Barnes Akathisia scores in either group. There were no elevations in plasma prolactin levels with aripiprazole compared to placebo. No clinically important cardiac risks were associated with aripiprazole. Weight gain associated with aripiprazole was comparable to placebo.

Conclusion: Aripiprazole was demonstrated to delay the rate of and time to relapse in patients with chronic schizophrenia, doing so with a favorable safety and tolerability profile. Aripiprazole, therefore, represents an important addition to the current antipsychotic armamentarium.

P.4.E.034 SWITCHING TO ARIPIPRAZOLE MONOTHERAPY

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Objectives: To assess the safety and tolerability of switching patients from current antipsychotic therapy to aripiprazole, a newly developed antipsychotic, with a unique mechanism of action (dopamine-serotonin system stabilizer). The impact on efficacy was also evaluated.

Methods: This multicenter, randomized, 8-week, open-label Phase III study involved 311 patients with chronic, stable schizophrenia or schizoaffective disorder who had received monotherapy with a typical (haloperidol or thioridazine) or atypical (risperidone or olanzapine) antipsychotic for ≥1 month. Patients were randomized into 3 groups: Group 1 – Immediate initiation of 30 mg/day aripiprazole with simultaneous abrupt discontinuation of current antipsychotic (n=104), Group 2 – Immediate initiation of 30 mg/day aripiprazole while tapering off current antipsychotic over 2 weeks (n=104), Group 3 – Titration of aripiprazole over 2 weeks (from 10 mg/day to 30 mg/day) while tapering off current antipsychotic (n=103).

Results: Safety and tolerability results were similar across treatment groups. There were no differences in discontinuations due to adverse events across the three groups. Antipsychotic efficacy was maintained in all groups throughout the study and improvement was seen from baseline in PANSS-total, -negative, and -positive subscales, and CGI-Improvement Score.

Conclusions: Switching to aripiprazole is safe and well-tolerated and can be initiated at an efficacious dose without having to gradually increase the dose of aripiprazole.

P.4.E.035 PHARMACOKINETICS AND SAFETY OF ARIPIPRAZOLE AND CONCOMITANT MOOD STABILIZERS

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Objective: To assess the pharmacokinetic and safety profile of aripiprazole, an antipsychotic with a unique pharmacologic profile of dopamine D_2 partial agonism, serotonin $5HT_{1A}$ partial agonism, and $5HT_{2A}$ antagonism, when coadministered with lithium or divalproex sodium.

Methods: Two open-label, sequential treatment design studies were conducted in chronically institutionalized patients with schizophrenia or schizoaffective disorder requiring treatment with lithium (n=7) or divalproex sodium (n=6). Patients received aripiprazole 30 mg/day on Days 1–14 and aripiprazole with concomitant therapy on Days 15–36. Lithium was titrated from 900 mg until serum concentrations reached 1.0–1.4 mEq/L for ≥5 days. Divalproex sodium was titrated to 50–125 mg/L.

Results: Coadministration with lithium increased mean C_{max} and AUC values of aripiprazole by about 19% and 15%, respectively, while the apparent oral clearance decreased by 15%. There was no effect on the steady state pharmacokinetics of the active metabolite of aripiprazole. Coadministration with divalproex sodium decreased the AUC, C_{max}, and C_{min} of aripiprazole by 24%, 26%, and 22%, respectively, with minimal effects on the active metabolite. Spontaneous adverse events reported with coadministration of aripiprazole and therapeutic doses of lithium or divalproex sodium were consistent with those observed with monotherapy of aripiprazole. There were no clinically relevant electroencephalographic changes.

Conclusion: Aripiprazole can be administered safely with therapeutic doses of lithium or divalproex sodium in patients with schizophrenia or schizoaffective disorder.

P.4.E.036 ILOPERIDONE ADMINISTERED TWICE-DAILY OR ONCE-DAILY IS WELL TOLERATED: A PROSPECTIVE DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, STUDY

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Objective: To compare the safety, tolerability and efficacy of bid and qd dosing regimens of iloperidone with haloperidol in patients with chronic schizophrenia.

Method: Patients (n=120) were randomized in a 2:2:1 ratio to receive bid iloperidone (12mg/d), employing either alternate day or daily titration schedules, or bid haloperidol (15mg/d). Patients were maintained on these doses until Day 28, after which the iloperidone patients were re-randomized to receive either iloperidone 4 mg bid or 8 mg qd from Days 29 to 42. The dosage could be increased to 12 mg/d after Day 35 if required. The PANSS was used to assess efficacy.

Results: Both bid and qd dosing regimens were generally well tolerated and the dropout rate due to AE's was similar in all groups (6–9%). Iloperidone was not associated with an increase in EPS, and concomitant use of benztropine was low in both bid and qd groups (4% each, compared with 64% in the haloperidol group). Efficacy achieved during the first four weeks of treatment was maintained at Day 42 in both dosing groups. There were no significant differences between groups on the PANSS at any timepoint.

Conclusions: Both qd and bid dosing of iloperidone were safe and well tolerated. The incidence of EPS was low with iloperidone compared to haloperidol. There was no loss of efficacy in switching from bid to qd dosing of iloperidone.