Abstract

It has been suggested that Mismatch negativity (MMN) generators lie in temporal and frontal cortices and that these generators show separate time courses in normal healthy subjects. However, little is known about the temporal association of MMN multiple generators in schizophrenia, although aberrant fronto-temporal connectivity is emerging issue in the pathophysiology of schizophrenia. The aim of this study is to investigate the temporal relationship of MMN multiple generators, which may reflect aberrant fronto-temporal functional connectivity in schizophrenia.

The present study assessed duration-deviant MMN using high density electroencephalography during passive oddball task in 29 patients with schizophrenia, 40 subjects at clinical high risk (CHR) for psychosis, and 47 healthy control (HC) subjects. Individual realistic head model, incorporating anatomical data from each individual's magnetic resonance image, was constructed. Minimum L2 norm algorithm was used to generate MMN current source density (CSD) model of MMN response over time. The strength of CSD and its time course were compared across groups.

Patients with schizophrenia and CHR subjects showed reduced MMN CSD strength compared to HC subjects in both frontal and temporal cortices. We also found significant time difference between temporal and frontal MMN generators in both CHR and HC groups, indicating that frontal MMN generators were activated later than temporal MMN generators. However, normal sequential generator activity was not found in patients with schizophrenia, with significantly increased variability of generator time behavior. In conclusion, schizophrenia patients showed both reduced and aberrant generator activity, while CHR subjects only showed reduced generator activity with relatively normal time behavior. Our findings suggest that aberrant fronto-temporal connectivity may emerge after the frank psychotic episode and may demarcate boundary between overt and early psychosis state.

PM511

Determinants of Caregiver Burden in Family Carers of Asian Patients with Schizophrenia treated with Paliperidone Palmitate 3-monthly injectable

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Abstract

Objective: Caregiving-associated burden in schizophrenia and its assessment require cross-cultural validation to identify risk groups and family functioning. In a post-hoc analysis, data of two double-blind, phase-3 studies were pooled to assess the level of perceived burden among carers of Asian patients with schizophrenia treated with paliperidone palmitate 3-month (PP3M) or 1-month long-acting injectable (LAI).

Methods: Carers (family member/friend in contact with patient for ≥1 hour/week) rated their burden of patient’s illness on 0–5 scale using 31-item Involvement Evaluation Questionnaire (IEQ), which contains four subscales (domains): tension (9-items), supervision (6-items) and worrying (6-items) and urgency (8-items).

Results: Among 412 carers (52% parents) of Asian patients with schizophrenia treated with paliperidone palmitate 3-month (PP3M) or 1-month long-acting injectable (LAI), IEQ scores improved for patients without relapse (mean [SD]: 30.8 [17.10]) to study end (24.0 [17.14]), predominantly relieving the burden associated with worrying (2.6 points) and urgency (2.7 points) domains. IEQ scores improved for patients without relapse (mean [SD]...
improvement: 7.8 \([18.64]\)] and worsened for those with relapse
(mean [SD] worsening: 0.9 \([15.52]\)]. This difference in relapse status
did not reach 0.05 statistical significance level, due to small
sample size in this analysis. Caregiver burden improvement
was significant in patients on prior oral antipsychotics post
switching to LAI with less leisure days impacted and less hours
spent in caregiving \((p<0.001)\). No significant relationship was
found between IEQ score improvement and any of the following:
factors: patient age, age of diagnosis, baseline long-acting
injectable (LAI) use, number and duration of prior psychiatric
hospitalizations (within 24 months prior to study entry).
Conclusion: A common pattern of burden was identified among
carers of Asian patients with schizophrenia, and this post hoc
analysis suggests that choosing an LAI treatment such as PP3M
or PP1M reasonably reduces the psychosocial burden associated
with caregiving.

PM512
The effectiveness of clozapine in reducing medical
costs associated with treatment-resistant schizo-
phrenia in Japanese patients
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Abstract
Objective: Treatment-resistant schizophrenia is costly. This
study evaluated treatment-cost changes following prescrip-
tion of clozapine in Japanese patients with treatment-resistant
schizophrenia.
Methods: Thirty-six patients were recruited; five were subse-
sequently excluded because clozapine was discontinued due to
side effects. Medical costs (Japanese yen: JPY) of hospital stay
and outpatient treatment were investigated separately, and
the total medical cost calculated as their sum. Treatment was
assessed at 6-month intervals, based on the month in which
clozapine therapy began. The 6-month period after starting clo-
apine therapy was defined as “0,” the prior 6-month period as
“-0.5 years,” and the subsequent 6-months as “0.5 years.” Per-
capita 6-month mean costs were calculated.
Results: Mean costs of hospital stay were JPY 253,306 at
-2.5 years, JPY 312,093 at -2 years, JPY 418,900 at -1.5 years,
JPY 442,247 at -1 year, JPY 450,538 at -0.5 years, JPY 507,850 at 0 years,
JPY 273,679 at 0.5 years, JPY 374,665 at 1 year, and JPY 267,414 at
1.5 years. Mean costs for outpatient treatment were JPY 9,807 at
-2.5 years, JPY 10,398 at -2 years, JPY 17,807 at -1.5 years, JPY
23,190 at -1 year, JPY 20,815 at -0.5 years, JPY 42,666 at 0 years,
JPY 58,496 at 0.5 years, JPY 60,617 at 1 year, and JPY 62,001 at
1.5 years. Mean total costs were JPY 36,438 at -2.5 years, JPY
41,028 at -2 years, JPY 96,831 at -1.5 years, JPY 144,495 at -1 year,
JPY 281,177 at -0.5 years, JPY 477,432 at 0 years, JPY 120,332 at
0.5 years, JPY 74,848 at 1 year, and JPY 72,999 at 1.5 years.
Conclusion: Costs of hospital stay and total costs gradu-
ally increased before starting clozapine therapy and peaked when
clozapine therapy began. Subsequently, outpatient costs slightly
increased, but total costs decreased notably. Clozapine therapy
is effective in reducing medical costs.

PM513
Clinical Pharmacology Study of Cariprazine with
Healthy Adult Japanese, Korean, Taiwanese, and
Caucasian Male Subjects
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Abstract
Objective: Cariprazine is a potent D_{3} and D_{2} receptor partial
agonist with preferential binding to D_{2} receptors. It has been
recently approved for the treatment of schizophrenia in USA
and is also under developing in Asia and EU. Cariprazine is
metabolized via the CYP3A4 and to a lesser extent via CYP2D6
pathways. In human the two active metabolites of cariprazine
are desmethyl cariprazine (DCAR) and didesmethyl cariprazine
(DDCAR). The effects of race/ethnicity on their pharmacokinet-
ics are unknown. Therefore, this study was designed to evalu-
ate the ethnic/racial difference in cariprazine pharmacokinetics
between Japanese, Korean, Taiwanese, and Caucasian.
Methods: This was a single-dose, randomized, open-label, paral-
lel-group study. Cariprazine 1 mg tablet was orally administered
to healthy adult Japanese, Korean, Taiwanese, and Caucasian
male volunteers under fasted condition. The pharmacokinetics
of cariprazine, DCAR and DDCAR were evaluated.
Results: 40 subjects (10 subjects in each ethnicity) were enrolled,
and all subjects were completed the study. C_{max} of cariprazine
in Korean and Taiwanese were similar to that in Japanese but
AUC_{last} were 41% and 33% higher in Korean and Taiwanese
than in Japanese, respectively. AUC_{last} of cariprazine was simi-
lar between Japanese and Caucasian but C_{max} was 44% lower
in Caucasian than in Japanese, partly due to larger body weights
for Caucasian. C_{max} and AUC_{last} of DCAR were approximately
the same or slightly lower in Korean and Taiwanese than in
Japanese, and were lower in Caucasian than in Japanese. C_{max}
and AUC_{last} of DDCAR tended to be comparable to or slightly
lower in Korean, Taiwanese, and Caucasian than in Japanese.
Conclusions: Between Japanese and each race/ethnicity, there
were small differences in the exposure to cariprazine, DCAR and
DDCAR. However, the distribution of variations in individual
values for each pharmacokinetic parameter was almost over-
lapped. This suggests that there were no major pharmacokinetic
differences among the races/ethnicities studied.

PM514
DRD2, 5-HT1A, and 5-HT2A gene polymorphisms
and clinical factors modulate aripiprazole efficacy in
different symptom dimensions of schizophrenia
DRD2, 5-HT1A, and 5-HT2A gene polymorphisms and clinical
factors modulate aripiprazole efficacy in different symptom
dimensions of schizophrenia
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Abstract
Objectives: Aripiprazole acts as a partial agonist at dopamine
D_{2} and serotonin 1A \((DRD2, 5-HT1A)\) receptors, and as
an antagonist at serotonin 2A \((5-HT2A)\) receptors. The current
study aims to examine the possible association between genetic
variants \((DRD2/ANKK1 Taq1A (rs1800497), 5-HT1A
C-1019G (rs6295), and 5-HT2A T102C (rs6313)) polymorphisms) and
clinical factors on the therapeutic response to aripiprazole
in Han Chinese hospitalized patients with acutely exacerbated
schizophrenia.
Methods: After hospitalization, the patients \((n=128)\) were given
a 4-week course of aripiprazole. Patients were genotyped for