Effect of the neuroprotective peptide davunetide (AL-108) on cognition and functional capacity in schizophrenia☆

Daniel C. Javitt a,⁎, Robert W. Buchanan b, Richard S.E. Keefe c, Robert Kern d, Robert P. McMahon b, Michael F. Green d, Jeffrey Lieberman e, Donald C. Goff f, John G. Csernansky g, Joseph P. McEvoy c, Fred Jarsoke h, Larry J. Seidman i, James M. Gold b, David Kimhy e, Karen S. Nolan a, Deanna S. Barch g, M. Patricia Ball b, James Robinson a, Stephen R. Marder d

a Nathan Kline Institute for Psychiatry Research, Orangeburg, NY, United States
b Mary Washington Psychiatric Research Center, Cantonsville, MD, United States
c Duke University Medical Center, Durham, NC, United States
d University of California, Los Angeles, Los Angeles, CA, United States
e Columbia University Medical Center, New York, NY, United States
f Massachusetts General Hospital/Harvard Medical School, Boston, MA, United States
g Washington University, St. Louis, MO, United States

1. Introduction

Schizophrenia is a severe neuropsychiatric disorder associated with structural as well as neurochemical brain pathologies (Crespo-Facorro et al., 2009; Bhojraj et al., 2011; Johnstone et al., 2011). Although numerous compounds are currently under development to target neurochemical abnormalities in dopaminergic, glutamatergic, cholinergic and other brain systems, relatively few compounds directly target structural pathology or related genetic pathways. The present study investigates effects of the novel neurotrophic peptide davunetide in the treatment of cognitive impairments in schizophrenia.

Davunetide is an intranasal drug presently under development for treatment of Alzheimer’s disease (AD) and progressive supranuclear palsy (PSP). Davunetide contains NAP, an 8 amino-acid peptide (Asn-Ala-Pro-Val-Ile-Pro-Gln; NAPVSIPQ, MW = 824.9) fragment of the much larger Activity-Dependent Neuroprotective (ADNP) Protein (Gozes et al., 2009). NAP functions in animal models of AD and PSP by interacting with microtubules to promote neurite outgrowth (Gozes and Divinski, 2007; Vulih-Shultzman et al., 2007; Kushnir et al., 2008; Gozes et al., 2009). In schizophrenia, neurocognitive deficits are also reliably associated with dendritic impairments (Glantz and Lewis, 2000; Kaniya et al., 2005; Glantz et al., 2006; Goldman...
et al., 2009; Carey, 2010), suggesting potential relevance of this mechanism to schizophrenia as well as AD/PS (Merrenelnder-Wagner et al., 2010). Furthermore, several genes associated with schizophrenia such as NRGI, Akt, and DISC1 function largely to modulate neurite outgrowth (Callicott et al., 2005; Kamiya et al., 2005; Shen et al., 2008; Young-Pearse et al., 2010; Johnstone et al., 2011; Lee et al., 2011), suggesting that this mechanism may target core neurogenetic disturbances in schizophrenia.

To be approved for treatment of cognition in schizophrenia, compounds must show efficacy not only on at least one domain of a standardized neuropsychological battery but also on a co-primary measure of functionally meaningful cognition (Buchanan et al., 2010). In the present study the MATRICS consensus cognitive battery (MCCB) (Nuechterlein et al., 2008) was used to assess neurocognition. Two potential co-primary measures of functionally meaningful cognition (Green et al., 2011) were also included: the UCSD Performance-based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (Keefe et al., 2006).

In phase 1 studies, davunetide has been found to have a benign safety profile at doses of up to 30 mg/d. In the present study, two daily doses of davunetide were used: 5 mg (5 mg QD) and 30 mg (15 mg BID). The 5 mg dose was selected on the basis of preclinical pharmacology as corresponding most closely with the dose used in effective preclinical studies (Matsuoka et al., 2007). The 30 mg dose was selected as the maximum tested dose in phase 1 studies. For the present study, therefore, we hypothesized that the 5 mg dose would show greatest efficacy. In addition, the study was conducted within the framework of FDA-MATRICS-NIMH recommendations for clinical trial designs for potential neurocognitive enhancing agents (Buchanan et al., 2010).

As an initial pilot study of the mechanism, the present study was powered to detect only medium–large (0.5–0.8 SD) effect size changes and to determine overall treatment feasibility. However, even smaller magnitude changes may be clinically meaningful. For example, a d-score of .2 (small) is considered to represent the threshold for clinical detectability (Cohen, 1988; Rosenthal and Rosnow, 1991). Thus, in addition to significance a key goal of this study was to determine magnitude of change, expressed in effect size, in order to guide design of potential follow-up studies.

2. Methods

2.1. Subjects

Eighty six subjects were assessed for eligibility and 69 were randomized. Six were excluded prior to starting double-blind medication, leaving a sample of 63 subjects (41M/22F) who were enrolled across seven sites (Fig. 1). Groups were similar in age (placebo: 41.4 ± 10.4 yrs; 5 mg: 43.2 ± 10.5 yrs; 30 mg: 45.2 ± 8.2 yrs), education (placebo: 12.1 ± 2.7 yrs; 5 mg: 12.6 ± 2.2 yrs; 30 mg: 12.4 ± 2.7 yrs), and Wechsler Test of Adult Reading (WTAR) score (placebo: 26.1 ± 13.1; 5 mg: 32.0 ± 13.7; 30 mg: 28.6 ± 11.4).

Inclusion/exclusion criteria were implemented as proposed previously by the TURNS consortium (Buchanan et al., 2010). Briefly, clinically stable inpatients or outpatients age 18–60 were included. Inclusion criteria included treatment with second generation oral and/or first generation depot antipsychotics, average Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1961) hallucinatory behavior and unusual though content scores ≤ 5 and conceptual disorganization score ≤ 4, Simpson Angus Scale (SAS) (Simpson and Angus, 1970) total score ≤ 6, and Calgary Depression Rating Scale (CDR) (Addington et al., 1994) score ≤ 10. Patients had to be deemed capable of participating in neurocognitive testing and to have scores on the Wechsler Test of Adult Reading (Wechsler, 2001) ≥ 6.

Exclusion criteria included DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the last month, or a diagnosis of alcohol or substance dependence (other than nicotine) within the last 6 months. Subjects with a history of significant head injury/trauma or clinically significant medical or neurological disease were also excluded. Women of child bearing age were included only if using adequate birth control. Participation in a clinical trial of investigational medication within 60 days was also exclusionary.

Antipsychotic treatments were not changed during the trial. The most common medications were olanzapine (17/63, 27.0%), aripiprazole (15/63, 23.8%) and risperidone (11/63, 17.5%). Eleven (17.5%) patients were treated with injectable antipsychotics, including 5 with injectable risperidone. Three patients (2 placebo, 1 5 mg davunetide) were receiving lithium. All subjects gave informed consent. The trial was coordinated by the University of California, Los Angeles and approved by the UCLA IRB as well as by the IRB boards of the participating institutions (Clinicaltrials.gov registry #NCT00505765). The trial was conducted under FDA IND and oversight was provided by the NIMH Drug Safety and Monitoring Board.

2.2. Experimental drug protocol

Following screening, patients were entered into a 2-week stabilization phase during which baseline neuropsychological and symptom ratings were obtained. The primary outcome measure was the age- and sex-adjusted composite T score of the MCCB (Nuechterlein et al., 2008). MCCB T scores are standardized against a representative sample of the general population to have mean 50 and standard deviation 10. Secondary outcome measures included total scores from the UPSA (Heinrichs et al., 2006) and SCoRS (Keefe et al., 2006). Other assessments included the BPRS, Schedule for the Assessment of Negative Symptoms (Andreasen, 1984), Clinical Global Impression (CGI), CDRS, SAS and Abnormal Involuntary Movement Scale (Gharabawi et al., 2005).

Subjects who remained stable during the 2-week period were randomly assigned to low dose (5 mg), high dose (30 mg) intranasal (i.n.) davunetide or placebo. For low dose, 1 puff was administered daily (QD). For high dose (30 mg), 3 puffs were administered twice daily (BID). For the placebo group, one half were assigned to the low-dose protocol (1 puff QD) and one-half to the high dose (3 puffs BID). For statistical purposes, data were combined across placebo conditions. Medication was dispensed every two weeks. Compliance was determined by weight measure of returned insufflators.

Study duration was 12 weeks. MCCB, UPSA and SCOrS were obtained at weeks 6 and 12. For patients who terminated prior to study completion, results collected within 2 weeks of the next scheduled administration were used to assess outcome. Other clinical ratings and safety measures were obtained biweekly. An ECG was obtained at screening and study completion. Potential effects of nasal administration on olfaction were assessed using a 3-item version of the Smell Identification Test (Jackman and Doty, 2005). Potential for nasal irritation was assessed by visual inspection.

2.3. Statistical analyses

Analyses were performed using a mixed model analysis of covariance: follow-up score = baseline score + treatment + week + treatment × week. The primary outcome was estimated by the average adjusted treatment difference across week 6 and week 12 (main effect of treatment), with the treatment × week interaction term providing a post hoc test for changes in treatment effects between weeks 6 and 12. All three pairwise contrasts between treatment groups were of interest. To control Type I error rates while performing 3 pairwise comparisons, Westfall’s (1997) procedure was used (Westfall, 1997). Reliability of the MCCB across administrations was assessed using intraclass correlation coefficients (ICC).

Two-tailed statistics were used throughout. Values in text represent mean ± S.E. unless otherwise specified.
3. Results

Patient flow is shown in Fig. 1. The MCCB was the predesignated primary outcome measure. Other measures, including UPSA, were considered secondary.

3.1. MCCB

Baseline MCCB composite scores were approximately 30, reflecting a reduction of approximately 2 SD units below the population norm. Baseline MCCB composite score was somewhat lower in the davunetide 5 and 30 mg at baseline than in placebo, although differences were not statistically significant. There was no significant main effect of treatment (F = 0.81, df = 2.53, p = 0.45) or treatment x week interactions (F = 0.6, df = 2.51, p = 0.94) (Fig. 2a). In addition, estimated davunetide-placebo differences based upon the ANCOVA were not significant for either the 5 mg (t = 1.9, p = .13), 5 mg (t = 1.25, df = 54, p = 0.21, d = .34) or the 30 mg (t = 1.2, df = .78, df = 53.5, p = 0.44, d = .21) doses. Mean change across weeks was 4.6 ± 1.7 and 3.9 ± 1.1 in the 5 and 30 mg groups respectively, vs. 3.2 ± 1.1 points in the placebo group (Fig. 2b).

MCCB data by domain are provided in Table 1. The mixed model test for domain x treatment interaction was statistically significant (F = 2.14, df = 12, p = 0.023), suggesting significant variation in average treatment effects during follow-up among the seven cognitive domains. This was driven primarily by significant reduction in verbal working memory during treatment with 5 mg davunetide vs. placebo (t = 2.75, df = 5.1, p = .008), with no significant change in other measures (Supplementary Table 1).

The test–retest reliability of the MCCB was high, with an estimated ICC for the overall MCCB composite score of 0.93; ICCs for individual tests and domains ranged from 0.70 to 0.88 (Supplementary Table 2). Based upon the magnitude of difference and ICC, it was calculated that a minimum per-group sample size of 45–50 subjects would be required to obtain statistical significance given present pattern of results.

3.2. UPSA

There was a significant main effect of treatment on the UPSA in the mixed model ANCOVA (F = 3.26, df = 2.45, p = .048) with significant differential improvement in the 5 mg group (diff = 5.4 ± 2 points, t = 2.52, df = 45.5, p = .015, d = .74), but not the 30 mg group (diff = 3.3 ± 2 points, t = 1.62, df = 44.8, p = .11, d = .48) vs. placebo. The overall treatment x week interaction was not significant (F = .17, df = 2.44, p = .85), suggesting no significant difference in response between weeks 6 and 12 (Fig. 3a).
Mean change from baseline at week 12 was 8.9 ± 1.6 and 4.9 ± 4.4 points in the 5 mg and 30 mg groups, respectively, vs. 0.3 ± 2.0 points in the placebo group (Fig. 3b). UPSA scores were approximately 5 pts lower at baseline in the low dose davunetide group than in the other two groups. However, the difference was not statistically significant (t = 1.40, p = .17).

Test–retest reliability of UPSA was high (ICC = .84). As in prior studies, baseline MCCB composite and UPSA scores were strongly correlated (r = .77, n = 57, p < .005) (Supplementary Table 2).

3.3. SCoRS

The SCoRS provides separate measures for achieved functioning in daily life activities based on interviewer composite scores and for subject, informant and interviewer assessments of change (Table 2). There were no significant between-group differences in outcome as assessed by either interviewer (F = .39, df = 2.51.2, p = .68) or informant-rated change (F = .87, df = 2.37.6, p = .4). Furthermore, no significant treatment differences were seen on mean assessments of change, all of which remained close to 4 (“no change”) in each group.

3.4. Symptoms

There were no significant differences between treatments (F = 1.79, df = 2.49.4, p = .18) or treatment × week interaction (F = 1.30, df = 10.66.8, p = .25) for the BPRS total score (Table 3, top). For the SANS (Table 3, bottom), the treatment effect was non-significant (F = 0.95, df = 2.51, p = .59), but the treatment × week interaction for the SANS approached significance, with increased negative symptoms over time in the 5 mg group (F = 1.95, df = 10.72, p = .053).

Mean CDRS scores were low at baseline and remained so throughout the study. There was no significant evidence for treatment main effects (p = .78) or treatment × week interactions (p = .19). No significant suicidal thinking was observed in any group. CGI scores also showed no significant change either within or across weeks.

3.5. Safety measures

No significant changes were observed on any safety measures. No significant changes were observed on the SIT in any treatment group and no significant nasal irritation was observed. Self-reported restlessness (almost always rated “mild”) was the only side effect with significant differences in the percentage of patients reporting new onset or worsening among the treatment groups (placebo, 9.1%; davunetide 5 mg, 45.0%; davunetide 30 mg, 19%; p = 0.025).

4. Discussion

This is the first clinical study of davunetide, a putative neurite outgrowth stabilizer, in the treatment of schizophrenia. No significant change was observed in primary analysis of the MCCB data across study week.
In the present study, MCCB and UPSA scores correlated significantly at baseline ($r = .77$, $p < .005$), suggesting that they measure related constructs. Nevertheless, especially at the 5 mg dose, greater effect-size change was observed for UPSA ($d = .74$) than MCCB ($d = .40$), leading to significant change in UPSA ($p = .015$) but not MCCB ($p = .21$). The most likely explanation for this discrepancy is simply the random variability of effect-size measures determined based upon relatively small sample sizes. Given the correlation between measures, the most likely "true" effect-size change for both measures lies intermediate between the two values, and thus in the range of medium effect-size. However, further studies with larger sample sizes are needed to confirm the degree of change in both variables and further evaluate the relative sensitivity of MCCB and UPSA to treatment-related change.

Other explanations for the discrepancy between MCCB and UPSA change scores, however, also need to be considered. First, since variability was observed across MCCB domains (see Table 1, Supplementary Table 1), it is possible that specific domains contribute more to UPSA change than others. For example, the MCCB processing speed index, which showed a $d = .4$ effect-size change in favor of davunetide, may contribute disproportionately to prediction of global outcome measures such as unemployment in patients with schizophrenia (Kern et al., 2011). Similarly, off-setting changes were observed in the present study in visual learning vs. verbal working memory. Given that UPSA is visually based, the change in visual learning may have contributed disproportionately. However, validation studies of the UPSA have not found differential correlations with MCCB subscale scores cross-sectionally (Green et al., 2008). How longitudinal change in MCCB relates to longitudinal change in UPSA remains to be determined.

Another concern is the non-significantly lower baseline scores in the 5 mg davunetide vs. other groups in both MCCB and UPSA.

doses ($p = .45$). In contrast, a significant change was observed on the UPSA ($p = .048$), which is considered to measure functionally meaningful cognition. Based upon these results, it was calculated that a sample size of 45–50 subjects per treatment arm would be required to demonstrate a significant between-group effect on both UPSA and MCCB. Such sample sizes are within the scope of a typical phase 2 pharmacological development program and thus support continued feasibility of davunetide development for schizophrenia.

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Another concern is the non-significantly lower baseline scores in the 5 mg davunetide vs. other groups in both MCCB and UPSA.
However, in this study, an ANCOVA model was used with baseline score treated as a covariate. This approach limits the influence of baseline differences on estimates of statistical significance. For example, if a repeated measures design had been used, the estimated effect size of davunetide on UPSA would have been substantially higher (d = 1.05). Furthermore, in a parallel study with MK-0777 in the same patient population, a similar between-group discrepancy in baseline scores was observed with no resulting significant treatment effect vs. placebo (Buchanan et al., 2011). Thus, low baseline scores, of themselves, do not lead to improvement at retest on the UPSA, suggesting that current results cannot be attributed to baseline differences alone.

A second issue in this study was inclusion of the SCoRS along with UPSA as an alternative potential co-primary measure relating to functionally significant cognition. In this study, no significant treatment effect was observed on the SCoRS, in contrast to the UPSA. However, clinical experience with SCoRS is more limited than with the UPSA and its sensitivity to change remains unknown. SCoRS uses a different source of information than the UPSA (interview/informant ratings vs. performance on standardized tasks) (Green et al., 2008). Although it was expected that interview-based measures would intercorrelate with performance based measures, recent studies have found limited shared variance between the two approaches (Green et al., 2011).

A related statistical issue in the present study is whether significance levels should be corrected for the three potential outcome measures used in this study (MCCB, UPSA, SCoRS). In this case, neither the UPSA nor the MCCB results would be considered statistically significant. However, such correction was not proposed in the initial analysis plan and would decrease the power to detect a significant effect on any measure given the small sample size. Furthermore, such corrections would not alter the effect-size of change estimates, which are the principal guides to future studies with this compound/mechanism.

In summary, this is the first test of a treatment, davunetide, that targets structural deficits of schizophrenia instead of more traditional neurotransmitter receptor targets. In this early stage study, no significant between-group effect was observed on MCCB, but significant change was observed on the UPSA functional co-primary measure. The sample size was small relative to those used in traditional phase 2/3 studies, so that ability to detect significant change was limited. However, the absolute magnitude of change on both MATRICS and UPSA, if confirmed in larger trials, would be sufficient to support registration for enhancement of cognition in schizophrenia in accordance with present FDA guidelines. Furthermore, the degree of change in the functional capacity measure used in this study, the UPSA, if confirmed, suggests that changes in cognition would be functionally meaningful, in accordance with FDA guidelines. Given the small sample size in this study, likelihood of replicating this effect in future studies cannot be determined. Based upon effect size considerations, however, future studies involving a minimum of 45–50 subjects per treatment arm are required to further test the utility of this mechanism in schizophrenia.

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Contributors

Daniel C. Javitt served as study PI and wrote the protocol in consultation with other authors. Drs. Buchanan, Lieberman, Goff, Cienansky, McEvoy, Jarosk and Marder served as site PIs. Drs. Keeffe, Kern, Green, Seidman, Gold, Kimhi, Nolan and Barch served as site neuropsychologists. Dr. McMahon designed and performed the statistical analyses. Ms. Ball and Mr. Robinson provided cross-site coordination and data management, respectively. Dr. Marder served as overall PI. All authors contributed to and have approved the final manuscript.

Conflict of interest

Javitt: Consulting: Sanofi, Solvay, Pfizer, Lundbeck, AstraZeneca, NPS Pharmaceuticals, Takeda, Sepracor, Schering Plough, Cypres Bio, Merck; Research support: Pfizer, Jazz, Equity: Glytech, AASI, Advisory Board: Pfizer.
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