Published in final edited form as:

J Clin Psychopharmacol. 2017 August ; 37(4): 447–451. doi:10.1097/JCP.0000000000000722.

Neurophysiological effects of bitopertin in schizophrenia

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Abstract

Purpose/Background—Deficits in N-methyl-D-aspartate receptor (NMDAR) function contribute to symptoms and cognitive dysfunction in schizophrenia, and are associated with impaired generation of event-related potential (ERP) measures including auditory mismatch negativity (MMN). Parallel studies of the NMDAR agonist D-serine have suggested that sensitivity of these measures to glutamate-based interventions is related to symptomatic and cognitive response. Bitopertin is a selective inhibitor of glycine transport. This study investigates effects of bitopertin on NMDAR-related ERP deficits in schizophrenia.

Methods/Procedures—Schizophrenia/schizoaffective disorder patients were treated with bitopertin (10 mg, n=29), in a double-blind, parallel group investigation. Auditory MMN served as primary outcome measures. Secondary measures included clinical symptoms and neurocognitive performance.

Findings/Results—No significant changes were seen with bitopertin for neurophysiological, clinical or neurocognitive assessments.

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Clinical trials registration: Clinicaltrials.gov: NCT01116830

Financial Disclosures:

Dr. Kantrowitz reports having received consulting payments within the last 24 months from Vindico Medical Education, Annenberg Center for Health Sciences at Eisenhower, Health Advances, LLC, SlingShot, Strategic Edge Communications, Havas Life and Cowen and Company. He has conducted clinical research supported by the NIMH, the Stanley Foundation, Merck, Roche-Genetech, Forum, Sunovion, Novartis, Lundbeck, Alkermes, NeuroRx, Pfizer and Lilly. He owns a small number of shares of common stock in GlaxoSmithKline.

Dr. Javitt reports having received consulting payments within the last 2 years from Pfizer, Autifony, Glytech, Sunovion, Forum, and Takeda. He has received research support from Roche. He holds intellectual property rights for use of NMDA modulators in treatment of neuropsychiatric disorders. He holds equity in Glytech, AASI, and NeuroRx, and serves on the advisory board of Promentis and NeuroRx. All other co-authors report no conflicts.

Implications/Conclusions—These findings represent the first assessment of the effect of bitopertin on neurophysiological biomarkers. Bitopertin did not significantly affect either symptoms or NMDAR-related biomarkers at the dose tested (10 mg). MMN showed high test-retest reliability, supporting their use as a target engagement measures.

Keywords

schizophrenia; electrophysiology; MMN; Glutamate; drug discovery

Introduction

All current treatments for schizophrenia, including both typical and atypical antipsychotics, function primarily by blocking dopamine (D₂) receptors. An alternative formulation for schizophrenia focuses on disturbances of brain glutamatergic neurotransmission, particularly at N-methyl-D-aspartate-type glutamate receptors (NMDAR)^{1,2}. NMDAR models of schizophrenia are based upon the ability of agents such as phencyclidine (PCP) or ketamine to induce symptoms and cognitive deficits closely resembling those of schizophrenia by blocking neurotransmission at NMDAR^{2–4}. In addition, glutamatergic models specifically account for impairments in the generation of neurophysiological measures, such as auditory mismatch negativity (MMN) and visual P1, which index local circuit dysfunction within sensory brain regions in schizophrenia. Deficits in auditory MMN generation^{5–8} and Visual P1⁹ have been replicated extensively in schizophrenia. MMN has previously been shown to index NMDAR function dysfunction^{6,9–12}, and appears to be unaffected by treatment with either typical or atypical antipsychotics^{9,13,14}, suggesting relative specificity for glutamatergic vs. dopaminergic mechanisms.

The present study evaluates utility of these biomarkers for evaluating target engagement and predicting outcome for bitopertin, a recently developed high affinity glycine type I (GlyT1) transport inhibitor¹⁵. Prior clinical studies with bitopertin have been mixed¹⁶. In an initial phase II study for persistent negative symptoms, bitopertin showed significant beneficial effect at doses of 10 and 30 mg/d in a per-protocol, but not intent-to-treat, analysis¹⁵. A follow-up phase III program targeting patients with predominant negative symptoms failed to show beneficial effects¹⁷. However, a highly significant ($p=0.0023$) effect was observed in 1 of 3 phase III studies targeting suboptimally controlled positive symptoms, although other findings were negative¹⁸, and further development has been abandoned.

The present project builds from a NIMH-funded program for D-serine, a direct agonist at the glycine modulatory site of the NMDAR¹⁹. Although results of individual clinical studies of D-serine have also been mixed²⁰, recent studies suggest significant beneficial effects on persistent negative symptoms in both adult^{21–23} and clinically high risk²⁴ populations. We recently observed significant improvement in symptoms ($d=0.8$) and MMN generation ($d=2.3$) after a 6 week treatment with D-serine²⁵, along with significant beneficial effects in on plasticity (learning) and MMN²⁶ after acute, intermittent (once weekly) D-serine treatment. The present report investigates effects of bitopertin at the dose that was most effective in the clinical development programs (10 mg), using similar neurophysiological methods as our prior, positive D-serine studies^{25,26}. We hypothesized that 1) MMN and

Visual P1 would be reliable, supporting the use of neurophysiological biomarkers for translational drug development in schizophrenia and 2) bitopertin would improve symptoms of schizophrenia to the extent that they induced objective benefit in MMN and Visual P1.

Methods and Materials

Subjects

Written informed consent for participation was obtained from all subjects. Subjects were aged 18–64 with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Subjects were psychiatrically stable as evidenced by a Clinical Global Impression (CGI) Change score²⁷ of 3–4 in the two weeks post screening visit, and were excluded for unstable medical illness, current clozapine treatment, psychotropic medication changes within 4 weeks, alcohol/substance abuse within past month or dependence within past six months. Functional impairment was determined by a GAF score between 31 and 50, inclusive, and a CGI-S score of ≥ 4 . Subjects were excluded for hemoglobin (Hb) < 130 g/L in males or < 120 g/L in females (because of potential bitopertin effects on erythropoiesis), and for Abnormal Involuntary Movement Scale global severity score > 3 (moderate) and/or Facial and Oral Movement items with a score > 2 (mild).

Study Design

This was a six-week, single-center, randomized, double-blind, placebo-controlled, two-arm parallel study in which subjects were randomized in a 3:2 ratio to fixed dose bitopertin (10 mg) versus placebo conducted at the Nathan Kline Institute, Orangeburg, NY. All subjects were receiving a stable dose of antipsychotic medications for ≥ 4 weeks.

Outcomes

MMN and Visual P1 were obtained using previously described methods^{9,25}, and assessed at baseline and at the end of treatment, collected in a single session per day. Symptom assessments were performed biweekly using the Positive and Negative Symptom Scale (PANSS) total and five-factor scores²⁸. The MATRICS consensus cognitive battery (MCCB) (minus the social cognition domain)²⁹ was used for neurocognitive assessment, administered before and after each treatment phase.

Statistical Analysis

Subjects were compared between randomized groups with respect to baseline characteristics using χ^2 test for categorical and 2-samples t-test for continuous variables. Linear mixed effects models³⁰ were used, and included indicators for treatment (bitopertin or placebo), and adjusted for the baseline levels of the outcomes. Since PANSS was measured repeatedly over the course of treatment, we included time by treatment interactions. In addition to random subject intercepts, these mixed effects models included random subject slopes to account for the correlation between the repeated bi-weekly assessments of subjects' symptoms. Between-group effect-sizes were calculated using Cohen's d expressed in SD units. Values in the text are Mean $\pm$ SD unless otherwise specified.

Results

Sample Description (Figure S1)

Twenty-nine subjects were enrolled (bitopertin: 17 and placebo: 12). Two patients in the bitopertin group were prematurely withdrawn from treatment because of non-serious adverse events, yielding 27 completers. There were no demographic differences between bitopertin and placebo groups, and all subjects were receiving antipsychotic medications (Table 1). In comparison to prior positive bitopertin studies^{15,18}, which limited chlorpromazine equivalents (CPZE)³¹ to <600 mg, CPZE for the present study were higher.

Outcomes

Voltage-topography distribution was similar to, but reduced compared to controls (Figure S2) with strong test-retest reliability across sessions (Cronbach α : MMN=0.75; P1=0.87) at our center. No significant treatment-by-deviant effect was seen for MMN ($F_{2,49,6}=0.6$, $p=0.55$) across deviants, nor for frequency ($F_{1,24}=0.01$, $p=0.94$, $d=0$), duration ($F_{1,24}=1.5$, $p=0.23$, $d=-0.5$) or intensity ($F_{1,24}=0.02$, $p=0.89$, $d=0$) deviants individually (Figure S2, Table 2), nor in P1 across hemispheres ($F_{1,24}=1.1$; $p=0.31$, $d=-0.43$). Bitopertin treatment was not associated with significant treatment by time interaction in the PANSS total ($F_{1,85}=0.2$, $p=0.68$, $d=-0.18$), reflecting a non-significant ($2.5\pm14.2\%$) reduction in symptoms for bitopertin for PANSS (Table 2). Change in PANSS factor scores and the MCCB were also non-significant (Table 2). No clinically significant side effects were observed. Two patients assigned to bitopertin were withdrawn: one for hernia pain not related to study treatment, and one for abnormal LFT's possibly related to study treatment.

Relationship between CPZE and outcomes

Given the relationship between antipsychotic dose and PANSS outcome in prior studies¹⁸, the relationship between CPZE and PANSS was assessed. Within the bitopertin group, a positive correlation was seen between final positive symptoms and CPZE ($r=0.51$, $p=0.044$). No significant correlation between CPZE and PANSS was seen in the placebo group ($r=0.2$, $p=0.46$).

Discussion

The present paper reports on the effects of bitopertin on NMDAR-based biomarkers in schizophrenia. Bitopertin did not significantly affect either symptoms or NMDAR-related biomarkers at the dose tested (10 mg). By contrast, we have previously observed significant interrelated effects of the glycine-site agonist D-serine on both symptoms and MMN^{25,26}. The lack of change of MMN in the present study is consistent with lack of clinical effect, and thus suggests that MMN may have negative, as well as positive, predictive value in predicting efficacy of novel compounds. MMN may be useful as a functional target engagement biomarkers for translational drug development targeting the glutamate system³².

The small magnitude change observed with bitopertin is consistent with small magnitude improvements that have been observed with high affinity GlyT1 inhibitors such as such as AMG-747³³ or Org25935³⁴. Given our small sample, a potential small effect size change on

both symptoms and biomarkers cannot be excluded. Nevertheless, clinical results are markedly smaller than those we recently observed with D-serine using a similar design²⁵ or those that have been reported with the naturally occurring compound sarcosine (N-methylglycine), which serves as an antagonist of both GlyT1 and “System A” type Small Neutral Amino Acid (SNAT2) transporters. System A transporters are also targeted by therapeutic concentrations of clozapine³⁵, and thus may be a critical component of the sarcosine response. Nevertheless, future studies investigating sarcosine effects on neurophysiological biomarkers are required.

Several limitations of the present study need to be acknowledged. First, only a single dose of bitopertin was used. Thus, significant effects might have been obtained at lower or higher doses. However, the dose used is the dose that has proven most effective across the development program. Second, patients in general were on high doses of antipsychotic, with ~40% of subjects receiving treatment with multiple antipsychotics. In the recent suboptimal response program, patients receiving treatment with multiple antipsychotics showed less robust response than those receiving monotherapy. Thus, it is possible that the high baseline antipsychotic doses in our population may have obscured a beneficial clinical effect, especially on negative symptoms. Nevertheless, similar antipsychotic doses and polypharmacy was present in our recent D-serine studies^{22,25}, and thus cannot fully account for the differential findings in the present vs. the previous study. Third, the overall n was small, although significant results were seen with similar n’s in our recent D-serine studies^{22,25}. Finally, we did not investigate the potential utility of bitopertin in facilitating cortical plasticity²⁶, which may be another beneficial effect of NMDAR agonist-based treatment.

In summary, we have previously observed that D-serine, an NMDAR glycine-site agonist that improves negative symptoms across clinical studies, also increases MMN amplitudes during both chronic and intermittent use^{25,26}. The present study demonstrates that the high affinity GlyT1 inhibitor bitopertin, which has failed in recent clinical trials targeting negative symptoms, also failed to improve MMN in the present study. Future studies are needed to determine the basis for the differential clinical effects noted with direct agonists (e.g. glycine, D-serine) or with the GlyT1/SNAT2 inhibitor sarcosine vs. more recently developed high affinity GlyT1 antagonists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by an investigator initiated grant from F. Hoffmann-La Roche to DCJ. F. Hoffmann-La Roche had no role in the final analysis or decision to submit for publication. Data has been presented in part at the NCDEU 2015 annual meeting.

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Table 1

Baseline Demographics and outcome measures.

		Bitopertin^I (n=17)	Placebo^I (n=12)
Demographics	Age	40±11	43±12
	Male (%)	100%	92%
	In-patient (%)	94%	92%
	Age of 1st Treatment	23±8	22±5
	CPZ Equivalents	767±963	588±372
	% Antipsychotic polypharmacy ²	41%	50%
Biomarkers	MMN_Frequency	-0.71±0.8	-0.75±0.7
	MMN_Duration	-0.45±0.5	-0.58±0.6
	MMN_Intensity	-0.52±0.7	-0.38±0.5
	Visual P1	0.48±0.7	0.60±0.9
Symptoms (PANSS)	Total	73.4±7.9	75.8±8.3
	Positive	12.6±2.7	13.4±5.2
	Negative	16.5±4.1	16.8±6.4
	Cognitive	10.2±2.9	10.8±2.9
	Depression	13.3±3	11.7±3.4
	Excitement	7.1±2.7	8.2±2.6
Cognition (MCCB)	Total	35.2±6.9	39.2±11.7
	Speed of Processing	32±10.8	35.2±18.6
	Attention & Vigilance	32.4±12.5	40.8±17.5
	Working Memory	36±10.6	37.8±14.9
	Verbal Learning	37.7±9	40.9±8.7
	Visual Learning	36.8±11.7	37.2±15.1
	Reasoning & Problem Solving	36±4.8	43.5±10.8

^I Mean±SD or %² Bitopertin subjects were receiving the following antipsychotics alone or in combination: olanzapine 35%; haloperidol 18%; aripiprazole, fluphenazine, perphenazine, quetiapine, risperidone and ziprasidone 11% each; paliperidone 6%.

Placebo subjects were receiving the following antipsychotics alone or in combination: aripiprazole and risperidone 33% each; olanzapine and haloperidol 25% each; quetiapine 17%; fluphenazine, lurasidone and perphenazine 8% each.

Within group % does not add up to 100% due to antipsychotic polypharmacy.

Table 2Primary outcomes: Final scores by study (mean $\pm$ sd)

Treatment type [/]	Active	Placebo	Statistics (F/p)	Effect size (d)
Biomarkers				
MMN_frequency	-0.68 $\pm$ 0.5	-0.71 $\pm$ 0.8	0.0/0.94	0
MMN_duration	-0.30 $\pm$ 0.5	-0.53 $\pm$ 0.4	1.5/0.23	-0.5
MMN_intensity	-0.59 $\pm$ 0.7	-0.47 $\pm$ 0.4	0.0/0.89	0
Visual P1	0.42 $\pm$ 0.7	0.69 $\pm$ 1.0	1.1/0.31	-0.43
PANSS				
Total	72.4 $\pm$ 9.8	73.5 $\pm$ 8.9	0.2/0.68	-0.18
Negative	15.9 $\pm$ 4.2	15.1 $\pm$ 6.1	2.0/0.16	-0.58
Positive	12.2 $\pm$ 3.1	13.4 $\pm$ 5.4	0.93/0.34	0.39
Cognitive	10.4 $\pm$ 3.4	10.4 $\pm$ 2.8	0.28/0.60	-0.22
Depression	12.2 $\pm$ 2.8	11.6 $\pm$ 4.5	1.6/0.22	0.52
Excitement	7.7 $\pm$ 2.7	8.7 $\pm$ 2.9	0.4/0.85	-0.26
MCCB				
Total	35.2 $\pm$ 7.4	39.2 $\pm$ 11.5	0.0/0.89	0
Speed of Processing	33.2 $\pm$ 11.5	35.9 $\pm$ 16.2	0.0/0.99	0
Attention & Vigilance	32.8 $\pm$ 12.9	39.2 $\pm$ 16.0	0.0/0.99	0
Working Memory	33.8 $\pm$ 11.3	38.1 $\pm$ 12.6	1.8/0.2	-0.55
Verbal Learning	36.8 $\pm$ 5.7	40.8 $\pm$ 11.6	0.6/0.43	-0.32
Visual Learning	37.2 $\pm$ 9.2	38.5 $\pm$ 16.8	0.9/0.77	-0.39
Reasoning & Problem Solving	37.6 $\pm$ 8.1	42.5 $\pm$ 11.1	0.4/0.55	0.26

[/] n=16 for bitopertin active and n=11 for bitopertin placebo.