The NMDAR Antagonist Dextromethadone Increases Plasma BDNF levels in Healthy Volunteers Undergoing a 14-day In-Patient Phase 1 Study

Sara De Martin [1], Ottavio V. Vitolo [2], Galina Bernstein [3], Andrea Alimonti [4 and 5], Sergio Traversa [2], Charles E. Inturrisi [6], Paolo L. Manfredi [2]

1.Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy
2.Relmada Therapeutics Inc., New York, New York, USA
3.Syneos Health, Toronto, Canada
4.Department of Medicine, University of Padova, Padova, Italy
5.Institute of Oncology Research (IOR), Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
6.Department of Pharmacology, Weill Cornell Medical College, New York, New York, USA

Background

Brain-derived neurotrophic factor (BDNF) is widely expressed in the central nervous system and plays an important function in neuronal plasticity. BDNF has been investigated as a biomarker of treatment response in depression and has been implicated in the mechanism of action of ketamine, an N-methyl-D-aspartic acid receptor (NMDAR) antagonist with rapid anti-depressant effects in humans[1].

In a study of patients with treatment resistant depression (TRD), ketamine was found to significantly increase plasma BDNF levels in responders compared to non-responders 4 hours post-infusion[2].

Dextromethadone (d-methadone), the d-isomer of the dl-methadone racemic mixture used for the treatment of pain and addiction, is undergoing investigation for the treatment of depression and other neuropsychiatric diseases. In contrast with the racemic mixture, d-methadone is free from clinically relevant opioid activity at doses expected to exert NMDAR antagonistic activity in humans[3].

Preclinical studies on animal models standardized for testing response to investigational antidepressant drugs have shown that the activity of d-methadone is comparable to ketamine in all tested models (submitted)[4].

Methods

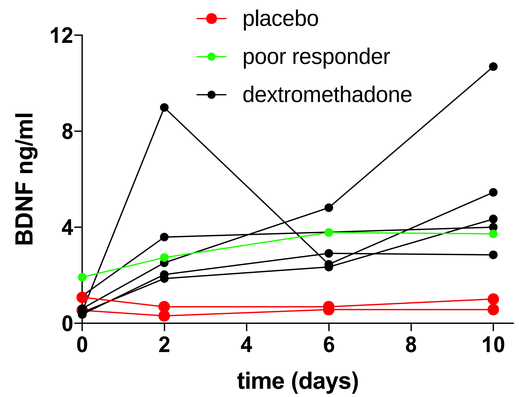
This study was part of a single-site, randomized, double-blind, placebo controlled phase 1 clinical trial of d-methadone administered orally for 10 days to healthy volunteers admitted for 14 days to a Clinical Research Unit (CRU).

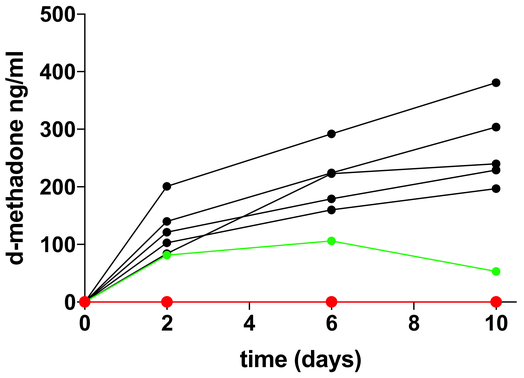
Sampling for testing of BDNF plasma levels from one study cohort was performed before any treatment and 4 hours after administration of d-methadone 25 mg (six patients) or placebo (two patients) on days 2, 6 and 10.

Plasma levels of BDNF were measured by means of an ELISA kit, following the manufacturer's instructions.

Quantitative determination of BDNF was carried out by standard calibration curves obtained with human recombinant BDNF at concentrations ranging from 0.066 to 16 ng/ml (n = 7), processed following the same protocol as the plasma samples. As expected, the calibration curves fitted an allosteric sigmoidal equation ($r^2 \geq 0.99$). Each concentration is the result of three independent determinations.

The statistical analyses were performed by means of GraphPad Prism 5.0 and SPSS software. The Wilcoxon Signed Ranks test was performed to compare BDNF concentrations before any treatment and 4 hours after administration of d-methadone or placebo on days 2, 6 and 10. We also checked a Spearman correlation between plasma d-methadone and BDNF concentrations.





	D-methadone AUC	Pretreatment BDNF	Day 10 BDNF	BDNF delta (day 10-day 0)
D-Meth Subj 1	2533	1.143	4.004	2.861
D-Meth Subj 2	1625	0.612	10.697	10.085
D-Meth Subj 3	1343	0.376	2.853	2.477
D-Meth Subj 4	1537	0.460	4.347	3.887
D-Meth Subj 5	1924	0.497	5.459	4.962
D-Meth Subj 6	774	1.922	3.733	1.811
Placebo Subj 1	0	1.086	1.012	-0,074
Placebo Subj 2	0	0.542	0.577	0,035

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Treatment Arm	Average Plasma BDNF ng/ml (±SD)	
	Pre-treatment	Post-treatment
d-Methadone	0.84 (0.60)	5.84 (2.83)
Placebo	0.81 (0.38)	0.79 (0.30)

p=0.028 at day 2, p=0.043 at day 6, and p=0.028 at day 10, all vs BDNF plasma levels before treatment.

Results

In the d-methadone treatment group, all subjects showed an increase in BDNF plasma levels post-treatment starting at least on day-2, with levels ranging from twice to 17 times the pre-treatment levels. By contrast, BDNF plasma levels remained unchanged in the 2 placebo treated subjects (plasma d-methadone level = 0).

Plasma BDNF levels measured at day-2 and day-10 were significantly correlated to the plasma levels of d-methadone when placebo subjects are included in the analysis.

The smallest increase on day-10 (twice the pre-treatment level) was seen in the study subject with the smallest day-10 d-methadone level, Cmax and AUC and the longest Tmax among all 6 treated subjects, consistent with a lower d-methadone pharmacokinetic disposition compared to other treated subjects.

d-Methadone did not cause psychotomimetic or clinically relevant opioid adverse events. No signs or symptoms of withdrawal were observed upon abrupt d-methadone discontinuation after the last study drug administration on day-10.

Conclusions

Administration of d-methadone 25 mg significantly increased BDNF plasma levels in healthy subjects undergoing a 14-day in-patient phase 1 study compared to placebo; the increase started at least on day-2 and persisted throughout day-10.

Despite its limitations, this study findings are consistent with the results of preclinical studies demonstrating d-methadone antidepressant-like activity in animal models of depressed behavior comparable to that of ketamine (in preparation).

Considering the lack of psychotomimetic and opioidergic adverse events and the overall acceptable tolerability and safety profile from two Phase 1 studies (in preparation), d-methadone has the potential to be a novel rapid acting antidepressant.

An undergoing Phase 2a study is assessing the tolerability, safety and rapid antidepressant efficacy of dextromethadone in patients with TRD.

References

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