NYX-2925, a novel N-methyl-D-aspartate Receptor Positive Allosteric Modulator, Showed Antinociceptive Activity in Functional Neuroimaging Evaluations Correlated with Improved Patient-Reported Pain and Fibromyalgia Symptoms

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Objective:

NYX-2925 is a novel *N*-methyl-*d*-aspartate receptor (NMDAR) positive allosteric-modulator in development for the treatment of supraspinal, centralized, chronic pain, including chronic painful diabetic peripheral neuropathy and fibromyalgia. This exploratory, placebo-controlled, single-blind, Phase 2 trial of NYX-2925 was conducted in females with fibromyalgia.

Background:

NMDAR-hypofunction in regions like the prefrontal cortex and the resulting neuroplasticity deficits altering frontocortical circuitry integral to pain perception have been strongly implicated in supraspinal, centralized, chronic pain. Enhancing activity in hypoactive regions might decrease activity in hyperactive regions like the insula and the anterior cingulate cortex (ACC) through modulations of activity across circuitry. The analgesic effect of NYX-2925 is hypothesized to result from increased NMDA receptor-mediated activity and reversal of neuropathy-induced hypoactivity of the medial prefrontal cortex observed in chronic, centralized pain states.

Design/Methods:

Twenty-two participants received two weeks of placebo, followed by two weeks of daily 20mg NYX-2925,followed by two weeks of daily 200mg NYX-2925. Participants underwent resting-state functional connectivity magnetic resonance imaging and proton magnetic resonance spectroscopy during the second week of each of three dosing periods.

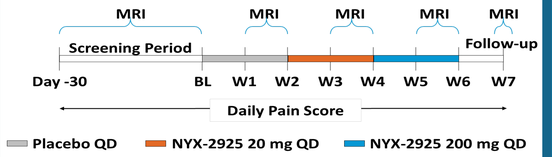
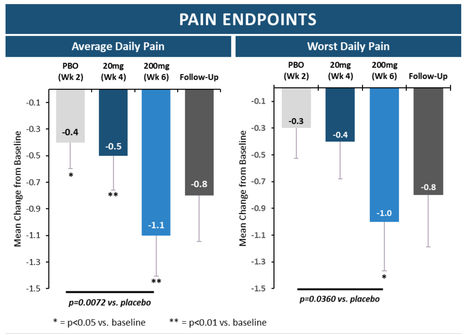


Figure 1.



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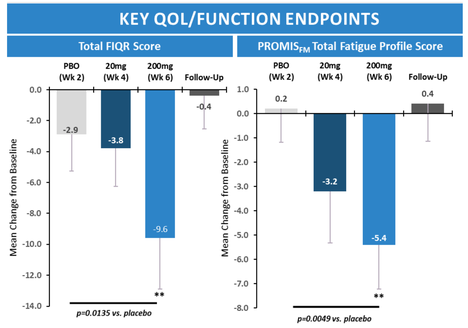

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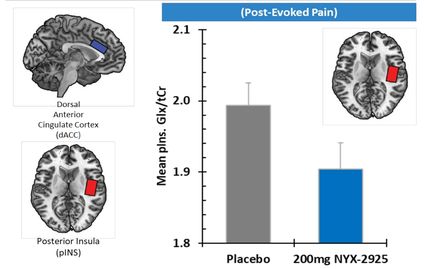
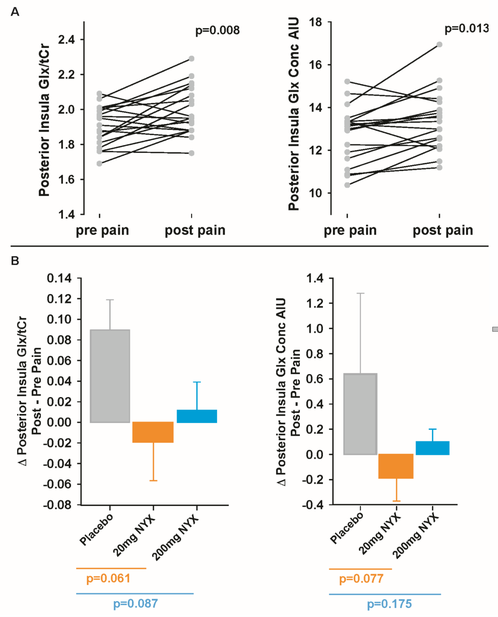


Figure 4.



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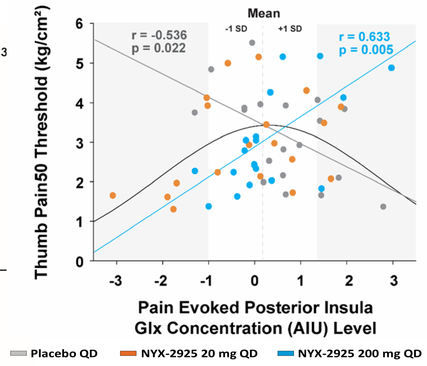


Figure 6.

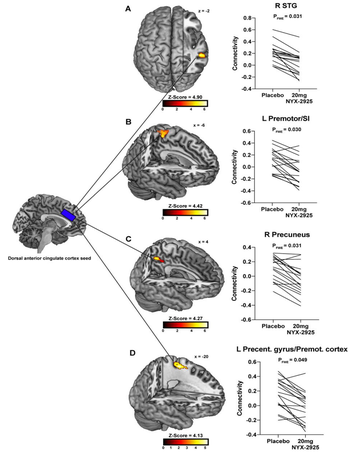
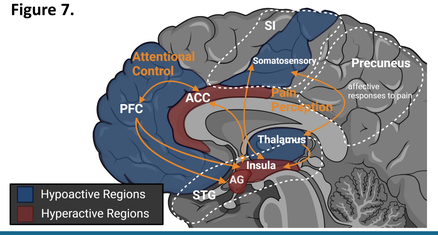


Table 1.

Seed Region	Connected Region	Size (mm³)	Cluster Z-score	$p_{FWE\text{-}corr}$	Peak Voxel Coordinates X	Y	Z
Placebo > 20 mg Dose							
Perigenual anterior cingulate cortex	L precuneus/postcentral gyrus	4968	4.12	***<0.00001***	-22	-5	74
Placebo > 200mg Dose							
Perigenual anterior cingulate cortex	R inferior frontal gyrus	1944	4.85	***0.008***	62	20	20
Medial prefrontal cortex	R anterior prefrontal cortex	2336	4.73	***0.003***	24	62	16
	R mid cingulate cortex	1440	4.07	***0.036***	10	-22	32

Figure 7.



Results:

Comparing placebo to post-NYX-2925 treatment resulted in reductions of clinical pain measures (Fig. 1) and symptoms of fibromyalgia, including fatigue, in the 200 mg/4 weeks treatment sequence (Fig. 2). This was accompanied by a reduced pain-evoked GLX increase, here expressed as a reduced GLX level post pain stimulation in the anterior insula (Fig. 3). Pre-post comparisons of pain-induced GLX changes, comparing NYX-2925 conditions with placebo in this region showed a trend for a reduction of the GLX signal (Fig. 4). This was accompanied by a reversal of the relationship between pain threshold and GLX-change (Fig. 5): Under placebo conditions, a reduction of subjective pain threshold corresponds to an augmented increase in pain induced GLX. After treatment with 200 mg NYX-2925, a reduction of pain threshold was associated with a reduced GLX signal. Finally, a reduced resting functional connectivity was observed between the perigenual ACC and the medial prefrontal cortex on the one hand and areas relevant for pain processing (Tab. 1) as well as between the dorsal ACC and areas related to the default mode network (Fig. 6).

Discussion:

Treatment with NYX-2925 leads to a time and/or dose dependent reduction in clinical ratings of pain and fibromyalgia and of physiological nociceptive pain signals, as expressed in the sensitivity of GLX changes to pain. A reduction in pain-related activity in the posterior insula and the reduced connectivity of the dorsal ACC may be a consequence of a moderating effect by an activation of antinociceptive areas in the PRC, in line with animal data (Fig. 7) (Ghoreishi-Haack et al., 2018).

No serious adverse events were reported.

Limitations:

The sequential design does not allow to differentiate time from dose effects. The relationship to mid-brain areas, in particular the periaqueductal gray, was not studied.

Conclusions:

Although these data were presented previously (Harte et al., 2019), they support further understanding of the role of NMDAR-hypofunction and restoration of circuitry integral to pain perception in treating chronic pain conditions like fibromyalgia. A Phase 2b double-blind, placebo-controlled study of 300 patients evaluating the safety and efficacy of NYX-2925 in fibromyalgia is ongoing.