Intranasal, Direct-to-Brain Drug Delivery for Cognitive Dysfunction in ME/CFS and Long Covid: Improved Efficacy, Safety, Cost, Comfort and Convenience over Systemic Drugs

Appendix: Bicameral (Neuro+Vascular) Therapy in Complex Disorders (e.g., PCS & ME/CFS)

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Abstract

Intravenous Immunoglobulin (IVIG) has had notably-favorable results in treating PCS (Post-Covid Syndrome; also called "Long Covid) and some efficacy in ME/CFS. **Challenges of IVIG** include costs (usually ~$6,000-8,000 / month), inconvenience (multiple-hour infusion sessions away from home) and discomfort (IV dosing).

Intranasal, direct-to-brain delivery successfully addresses these issues.

Of note is a recent patient series (n=10) from Bochum, Germany, where IVIG in PCS (Long Covid) patients improved fatigue (70% decrease of patients with symptoms), brain fog (67%), insomnia (67%), and listlessness (78%). Particularly for cognitive dysfunction (including brain fog and insomnia) and fatigue / listlessness, intranasal immunoglobulin (IN-IG) is emerging as a promising alternative to IVIG on the basis of

- **Efficacy:** Greater penetration to the brain (blood-brain barrier is circumvented, rather than penetrated)
- **Safety:** No injection-site reaction; virtually no systemic exposure
- **Cost:** ≥ 90% reduction in cost
- **Convenience:** One or two minutes at home vs. one or two multi-hour visits to an infusion center
- **Comfort:** Intranasal dosing (usually no irritation) vs. IV injection.

Intranasal, direct-to-brain drug delivery (circumventing, rather than penetrating the BBB) is an important option for molecules larger than 0.5 kilodaltons, which tend not to cross the BBB effectively – more so for larger molecules, such as peptides (insulin, 5.8 kDa) and antibodies (IG, 150 kDa). We work with a device that effectively delivers both to the CNS.

While IN-IG has yet to be used in a clinical trial for ME/CFS or PCS, a number of patients using IVIG for either neurodegenerative (e.g., Alzheimer's disease) or neuroinflammatory (e.g., PANS) disorders have switched from IVIG to IN-IG, with the following results:

- Immunoglobulin (IG) dosage and costs reduced at least 90%
- Cognitive symptoms treated at least as well, if not more effectively
- The drug/device combination is safe, convenient, and well-tolerated

We are therefore optimistic about IN-IG as an effective, affordable treatment in PCS and ME/CFS, particularly for cognitive symptoms.

Problem 1: Effective drug delivery to the brain is usually difficult and inconvenient – especially for large-molecule drugs

The blood-brain barrier (BBB) is highly effective at blocking toxins – but also blocks most potentially-therapeutic drugs. This makes it difficult if not impossible for >98% of small molecules and ~100% of large molecules to penetrate the CNS efficiently and effectively.[1]

An excellent example is the use of immunoglobulin (IG) in treating neuroinflammatory disorders. Intravenous immunoglobulin (IVIG) is often the preferred treatment for treating neuroinflammation in moderate and severe cases of PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)[2] but it has **significant drawbacks limiting use**

IVIG is Expensive: Frequently ~$6000-8,000 / month

Inconvenient: Multiple-hour infusions, sometimes needing two days

Uncomfortable: Intravenous administration

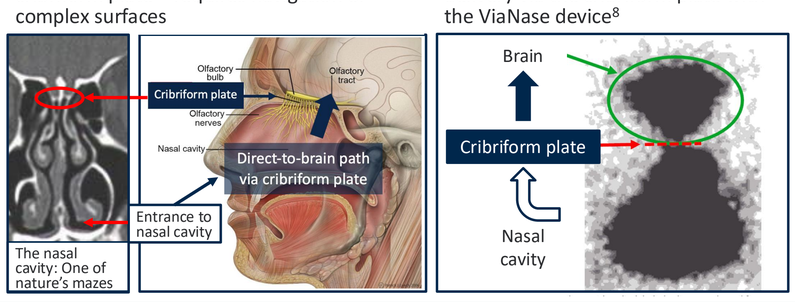
Solution 1: Intranasal, direct-to-brain drug delivery effectively accesses the CNS with drugs previously not available as CNS treatments

The ViaNase device (Kurve Therapeutics, Inc.; Seattle, USA) generates precisely-controlled, turbulent aerosols that can reach the top of the nasal cavity. It evidently has distinctive capability with larger molecules:

1. In a 2021 review of ~3,000 papers reporting intranasal drug delivery targeting the CNS,[3] the two most-cited papers for delivery of molecules >1 kDa were of insulin (5.8 kDa) with ViaNase. In both papers, cognition was improved vs. placebo in Alzheimer disease.[4,5]
2. IN-IG (intranasal immunoglobulin, 150 kDa)/ViaNase has been used safely and favorably at a California Alzheimer's clinic for nine years. Improvements are frequently evident in 1-3 months.[6]
3. Since late 2024, patients have used IN-IG / ViaNase in neuroinflammatory disorders, with notable improvements in PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome).

   In contrast to the weeks-to-months time scale with Alzheimer's, neuroinflammatory-disorder patients frequently see appreciable improvements within 24 hours.[7]

Direct-to-brain drug delivery – via passage along the olfactory nerves through the cribriform plate – requires navigation of complex surfaces



Study with radiolabeled saline showing intranasal, direct-to-brain delivery via the cribriform plate with the ViaNase device[8]

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Disclosures

Glenn Cornett is a co-founder and minor shareholder (<5%) of Kurve Therapeutics.
Glenn Cornett is a founder and significant owner or shareholder (>30%) of mplexity and Navitas Pharma.

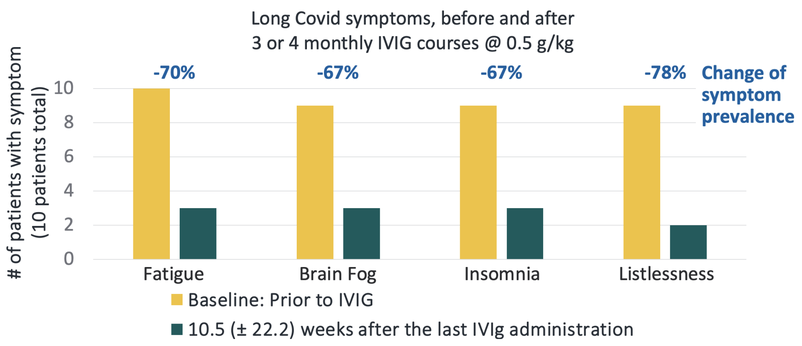
Problem 2: The financial burden of effective, large-molecule CNS treatments is significant

Example: IVIG for PANS, PCS and ME/CCFS

Due to poor penetration of the BBB, large-molecule drugs usually need large, expensive doses for treatment of CNS symptoms and disorders.

At 150 kDa, IVIG (intravenous immunoglobulin) provides an excellent example of large-molecule therapies that can be effective in certain CNS disorders but are expensive as systemically-administered CNS treatments.

1. PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome)
   A. As mentioned earlier, IVIG is often the preferred treatment for neuroinflammation in moderate and severe cases of PANS[2]
   B. In a study of US PANS patients using IVIG (N = 45), among those without insurance that covered ≥70% of expenses (N = 21, or 47% of the patients), at least one-third of families reported extreme stress (10 on scale of 1 to 10), 58% borrowed money, and 21% sold at least one major asset (e.g., a car) in order to pay for IVIG therapy. Even families with substantial insurance coverage withdrew savings (57%) or borrowed funds (26%) to cover care.[9]
   C. Monthly IVIG costs for PANS patients in Europe are ~€6,000.[7]
2. Long Covid
   A. IVIG has used with favorable results in cognitive symptoms of PCS. In a German case-control study, IVIG improved CNS symptoms of PCS, including fatigue, brain fog, insomnia and listlessness.[10]

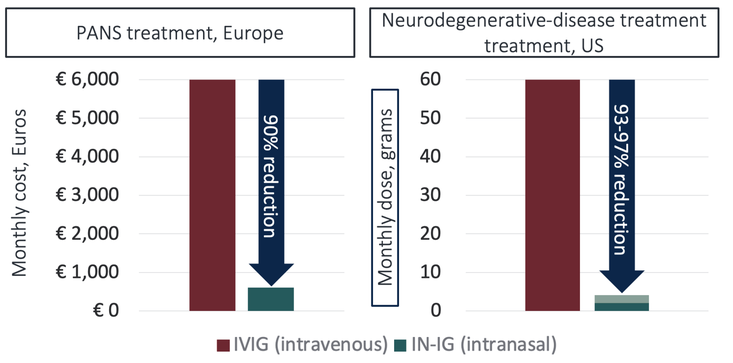


   B. This study used monthly courses of 0.5 g/KG, coming out to 35 g **(~$6,650 @ $190/g) for a 70-kg adult.**

Solution 2: Intranasal dosing of immunoglobulin reduces drug cost ≥ 90% vs. IVIG

1. At the Newport Beach, California clinic treating Alzheimer's patients with IN-IG, ViaNase-device use has reduced per-month IG use (vs. IVIG) from ~60g to 2-4g, a 93-97% reduction.[6]
2. In Europe, the switch to ViaNase intranasal delivery in PANS patients has reduced monthly costs by 90%, from ~€6,000 to €600, and in some cases to €150-300. This has made the treatment affordable for a large portion of families.[11]

≥ 90% dose-size / cost reduction in switching from IVIG to IN-IG (i.e., with ViaNase Device)



3. It is expected that cognitive / neuroinflammatory aspects of PCS and ME/CFS could likewise be treated cost-effectively by intranasal, direct-to-brain IG administration with the ViaNase device
   A. Cognitive symptoms of Long Covid and ME/CFS, similar to those of PANS, are due to neuroinflammatory processes
   B. Long Covid has had particularly-favorable results from multi-dose administrations of IVIG (once per month, 3-4 months)
   C. Costs for immunoglobulin (IG) treatment of PANS have been reduced ≥90% by conversion to intranasal treatment (i.e., with the ViaNase device); we expect similar efficiencies in PCS & ME/CFS.

Brief description of relevant organizations

Kurve Therapeutics develops drug products and technologies (including the ViaNase atomizer platform) with precisely-controlled aerosols for targeted delivery. Intranasal, direct-to-brain ("nose-to-brain" drug delivery a frequent application of this platform in treating CNS disorders and symptoms.

mplexity is a venture studio that originates and grows companies with drugs for CNS, CV, autoimmune and other disorders. mplexity develops approaches to bicameral (neuro+vascular) therapy.

The "neuro side" of mplexity's bicameral therapy predominantly involves intranasal, direct-to-brain drug-delivery technology from Kurve Therapeutics.

mplexity's "vascular-side" therapy is focused on the use of the eNOS-activating drug cicletanine. mplexity company **Navitas Pharma** owns the US IND (the most-up-to-date regulatory package for cicletanine) and certain global rights.

Kurve THERAPEUTICS

mplexity Complex Disorders / New Solutions

NAVITAS PHARMA

Poster QR code

Provocative hypothesis:

Treating neuroinflammation without repairing leaky endothelium can be like replacing rain-damaged furniture without repairing the roof.

Appendix

Bicameral (neuro+vascular) therapy: Addressing the complexity of disease

Complex, challenging disorders often have critical pathology outside their explicit therapeutic domains.

For example, post-infection disorders such as PCS or difficult-to-categorize syndromes such as ME/CFS have have critical CNS and CV components.

This complexity is sometimes explored by academic investigators, but frequently not addressed by industry, effectively de-railing opportunity for therapeutic advances

- **Vascular endothelial dysfunction (EnD)** is now acknowledged by leading academic investigators as a key driver of Alzheimer's and PCS
- ...but industry-sponsored activity vs. EnD in these disorders is scant

Bicameral therapy engages this complexity, delivering drugs separately to CNS and cardiovascular/systemic targets.

In PCS, brain fog has ongoing endothelial dysfunction (EnD) and cerebrovascular leakage.[17] Here is a neuro+vascular approach

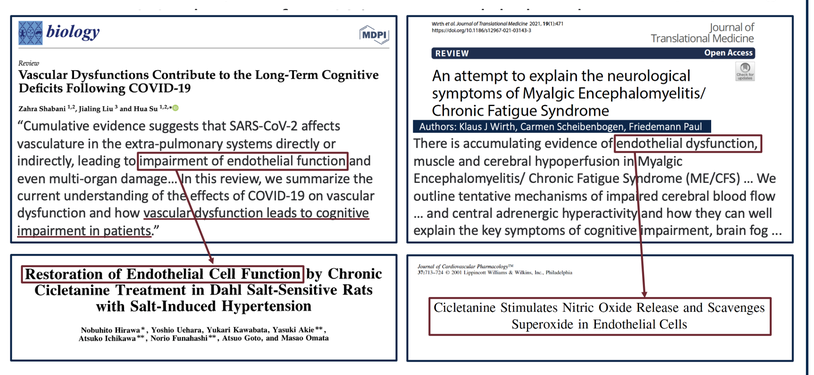
> Treat neuroinflammation with IN-IG

Intranasal, direct-to-brain delivery of immunoglobulin (IN-IG) has been effective in PANS at ≤ 1/10 the effective dose level of IVIG.

The success (and expense) of IVIG **vs. brain fog, insomnia, malaise and other CNS symptoms** in published PCS cases suggest a similar, positive role of IN-IG in PCS (and, hopefully, ME/CFS)

> Treat EnD with endothelial agent cicletanine

Cicletanine (CIC) addresses the root of endothelial dysfunction (EnD) by activating eNOS (endothelial nitric oxide synthase). CIC has an established safety and efficacy profile (please see below) in cardiovascular disease (including multi-year use in pediatric patients with heart defects) and is expected to be safe in PCS. We are preparing



→ **Cicletanine (CIC)** activity vs. **EnD** has been known for a while; unique target and mechanism recently characterized by mplexity/Navitas

Recent mechanistic insights also include

- % Sympatholytic and pro-parasympathetic activity putatively relevant to autonomic imbalance in PCS and ME/CFS
- % Reversal of NaK-ATPase inactivation has likely relevance in PCS

→ **Cicletanine:** Approved in France for hypertension; favorable safety

- % Well-tolerated in clinical trials (>10,000 patients)
- % On-market pharmacovigilance: <1 serious adverse event per 100,000 patient-months

→ **Cicletanine** is promising vs. **EnD** in Long Covid and ME/CFS

- % Addresses the root cause of **EnD** by activating eNOS (endothelial nitric oxide synthase) via a unique mechanism
- % Has favorable clinical data in several **EnD**-driven disorders (hypertension, heart failure, angina, diabetic kidney disease)
- % CIC therefore thought relevant to **EnD** in PCS and ME/CFS

Discussion with potential investigators is welcome: cornett@mplexity.com

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