Are critical world events confounding factors for clinical trials?

Steven D. Targum MD

ISCTM, Boston Massachusetts

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Steven D. Targum MD Disclosures

Current Professional Affiliations

Scientific Director, Signant Health

Chief Medical Officer, Functional Neuromodulation Inc (Minneapolis, MN)

Equity interests

Signant Health, Methylation Sciences Inc., EMA Wellness, Functional Neuromodulation Inc., PAX Neuroscience, XR Health

Consultation/CDA's within the past three years

Acadia Pharmaceuticals Inc, AZ Therapies, BioXcel Therapeutics, EMA Wellness, Denovo BioPharma, Epiodyne Inc., Frequency Therapeutics, Functional Neuromodulation Inc, Karuna Pharmaceuticals, Merck Pharmaceuticals, Navitor Pharmaceuticals, Neurocrine Bioscience, PAX Neuroscience

Are critical world events confounding factors for clinical trials?

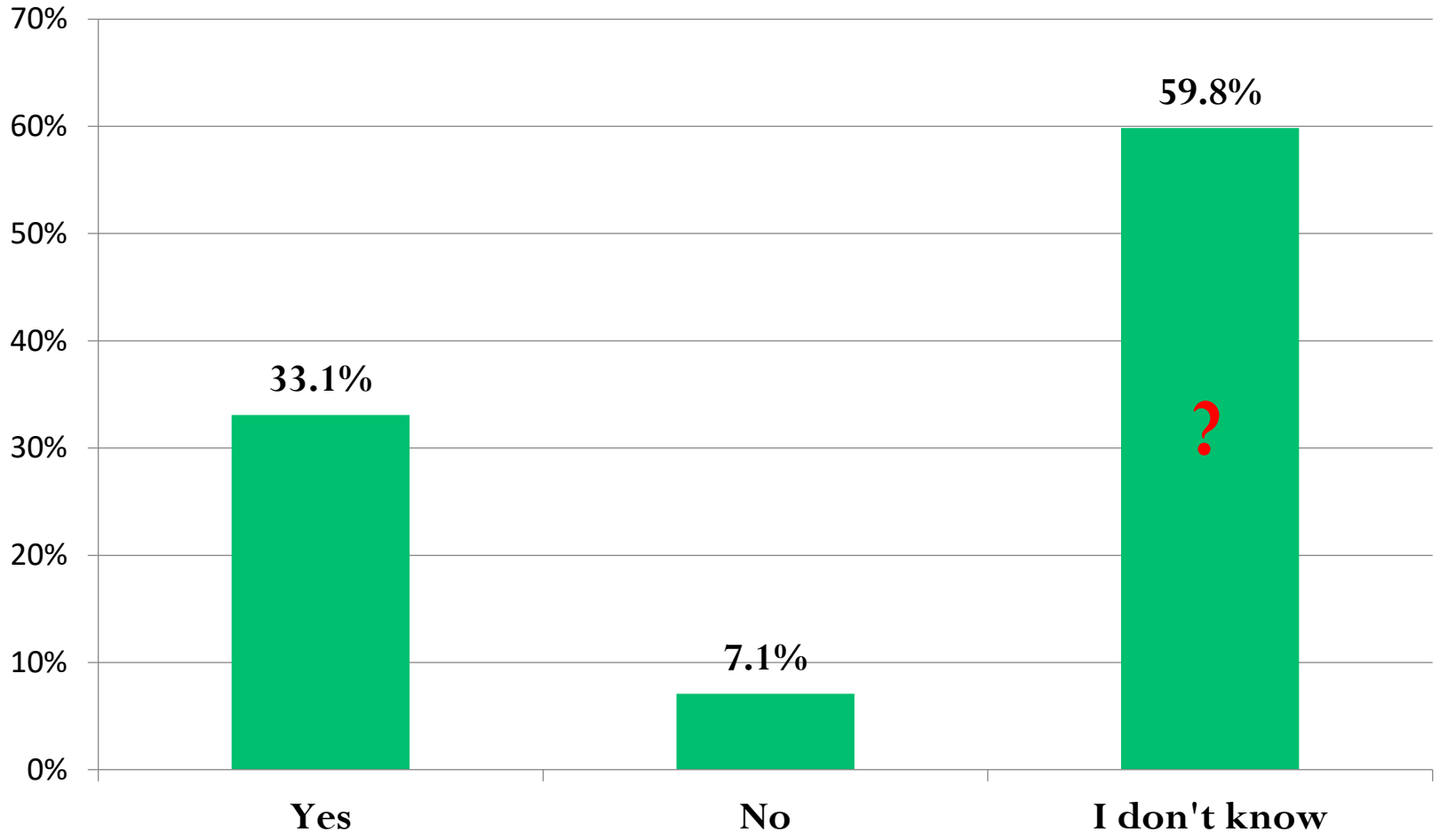
- The war in the Ukraine and the SARS-CoV-2 virus (COVID-19) pandemic have caused profound stress and may have contributed to increased worldwide neuropsychiatric illness.
- These events share common anxiogenic factors like:
  - The loss of control and personal freedom
  - Fear (both real and perceived)
  - Concern for the well-being of oneself and one's relatives
  - Isolation (quarantine)
- These and other confounding factors may contribute to the emergence or re-emergence of acute psychiatric disorders.
- **In this workshop, we'll examine the implications of critical world events for:**
  - **The execution of CNS clinical trials (recruitment, staff changes, missed visits)**
  - **The interpretation of results (regional differences, confounding etiologies)**

Results of an ISCTM Member Survey

conducted June-July 2022

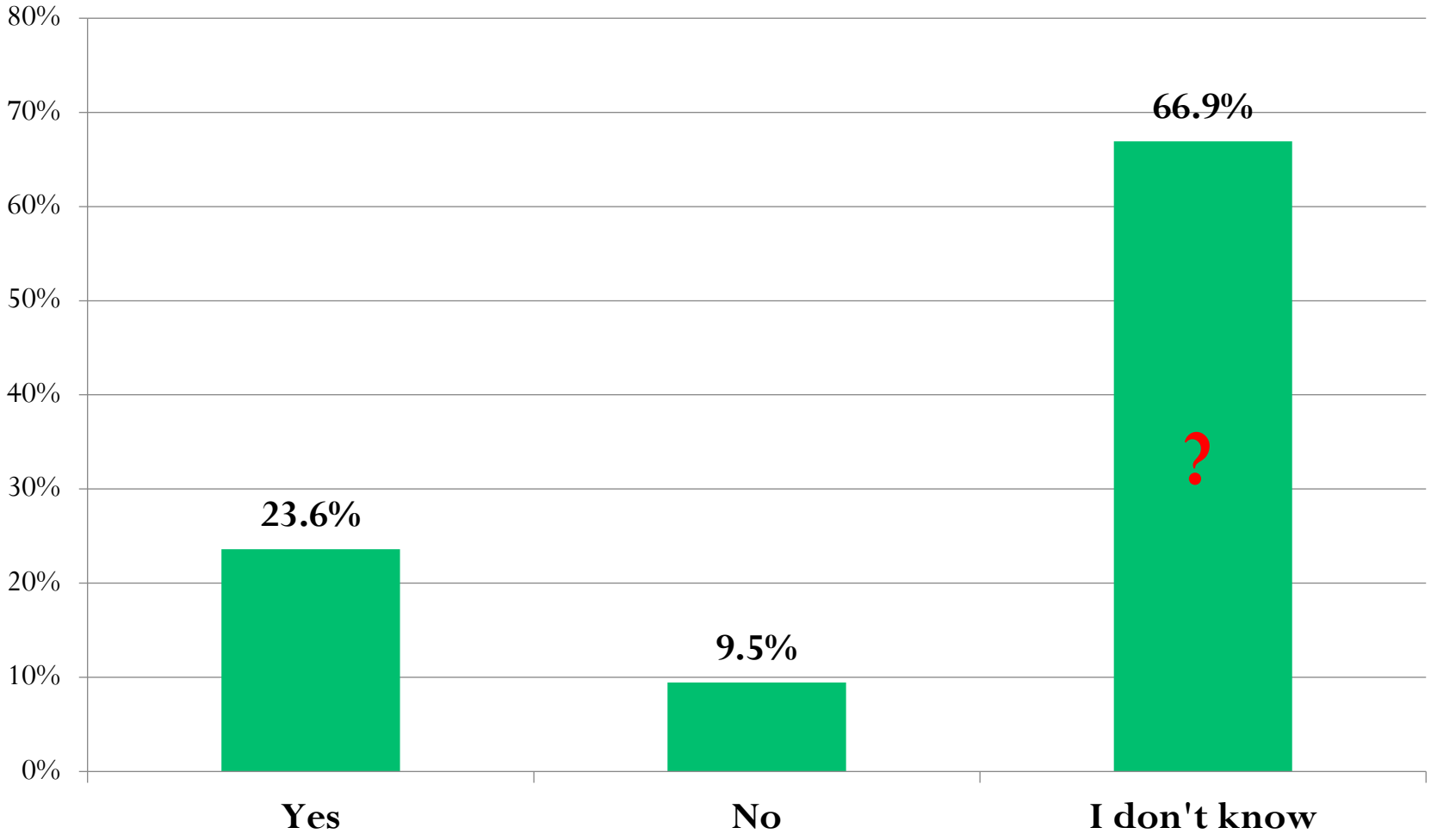
- 127 ISCTM members responded to a brief "opinion" survey about the impact of world events on clinical trials
  - 92% believed that world events have complicated the execution of clinical trials
  - 65% believed that world events have confounded the interpretation of study results
- Regarding the war in Ukraine:
  - 65% of respondents believed that the direct and indirect trauma of war can affect the interpretation of clinical trial results (28% said they did not know)
  - 69% responded that trials could not currently be conducted in the Ukraine (27% didn't know)
  - 64% responded that trials could not currently be conducted in Russia (27% didn't know)
  - Only 6% responded that trials could not currently be conducted in Poland (25% didn't know)
- Regarding the COVID-19 pandemic:
  - 93% responded that subject recruitment has been affected by the COVID-19 pandemic
  - >50% of ISCTM members **were unsure** about the direct effect of the COVID-19 virus on the trajectory of mood disorders or the response of COVID-related mood disorders to treatment

Is there a **different trajectory of illness** between COVID-19 and non-COVID related mood or anxiety disorder? (n=127)



Data from ISCTM survey conducted June-July 2022

Is there a **different treatment response** between COVID-19 and non-COVID related mood or anxiety disorders? (n=127)

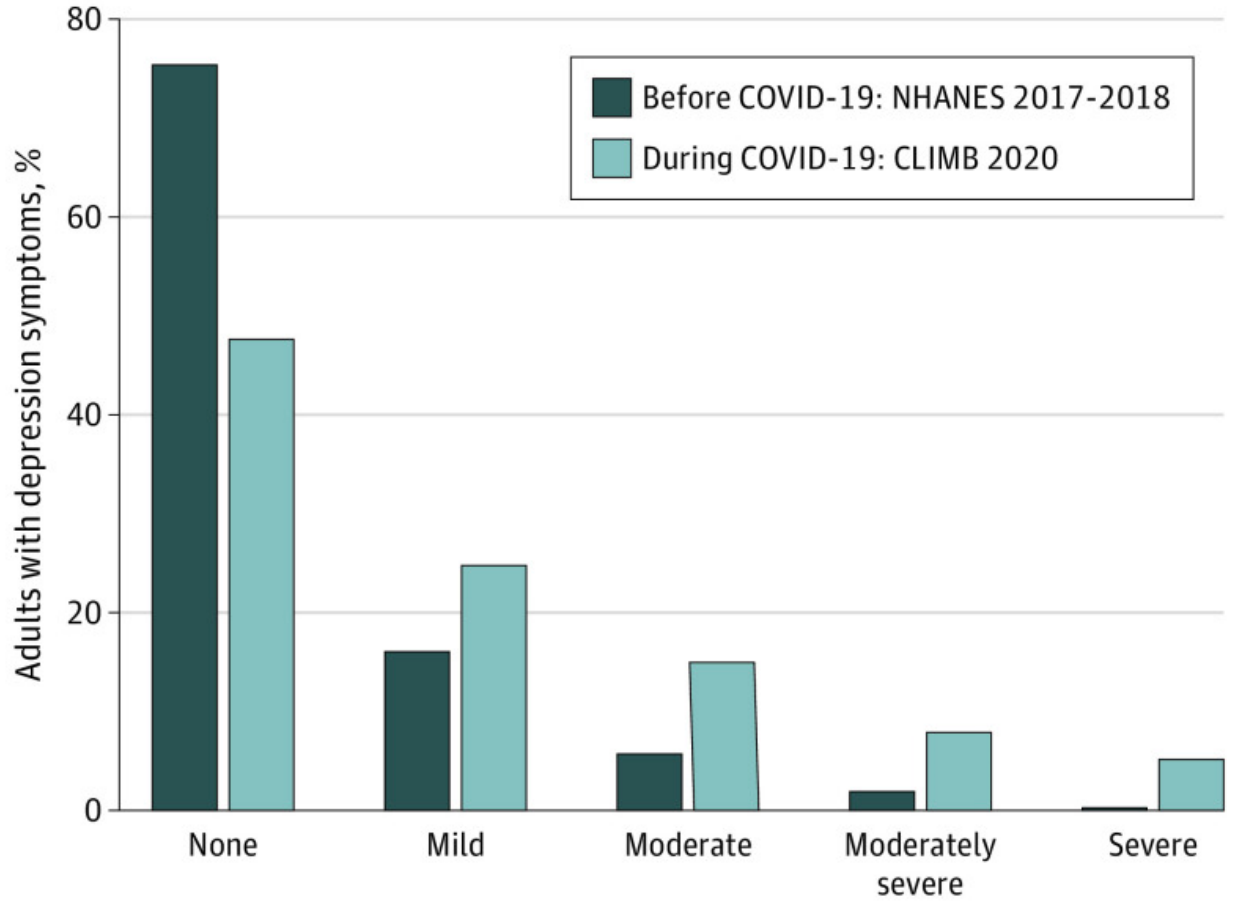


Data from ISCTM survey conducted June-July 2022

Interpretation of results
Psychiatric disorder and the COVID-19 pandemic

- Anxiety and depression have increased since the start of the COVID-19 pandemic.
  - A recent meta-analysis found that the pooled global prevalence of depression was 25% since the outbreak of COVID-19 compared to only 3.4% in 2017.
  - Numerous follow-up studies have documented that many post-COVID patients suffer from persistent anxiety, depression, fatigue, neurological, and neuropsychological symptoms.

Depression Symptoms in US Adults have increased since the start of the COVID-19 Pandemic (Ettman et al., 2020)



Before COVID-19 estimates from the National Health and Nutrition Examination Survey (NHANES) from 2017-2018. During COVID-19 estimates from the COVID-19 and Life Stressors Impact on Mental Health and Well-being (CLIMB) study collected from March 31 to April 13, 2020.

Depression symptoms categories were calculated using the Patient Health Questionnaire–9 (PHQ-9): none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (≥20). Percentages weighted to the population of noninstitutionalized US adults aged 18 years or older

COVID-19 induced psychiatric disorders may differ from more conventional non-COVID related psychiatric disorders

- The host immune response to the COVID-19 virus can generate a severe neuroinflammation with cerebrovascular effects that may be associated with the development of psychiatric disorders.
- Using real world data from people with influenza for comparison, Taquet and colleagues (2021) reported significantly more **first-ever diagnoses** of anxiety, mood, and psychotic disorders within 14-90 days following infection with COVID-19 (all $p < 0.0001$).
- It is not known whether these COVID-19 "induced" psychiatric disorders have the same etiology, illness trajectory, or treatment response as more conventional psychiatric disorders.

Taquet et al., 6-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021; 8: 416–27

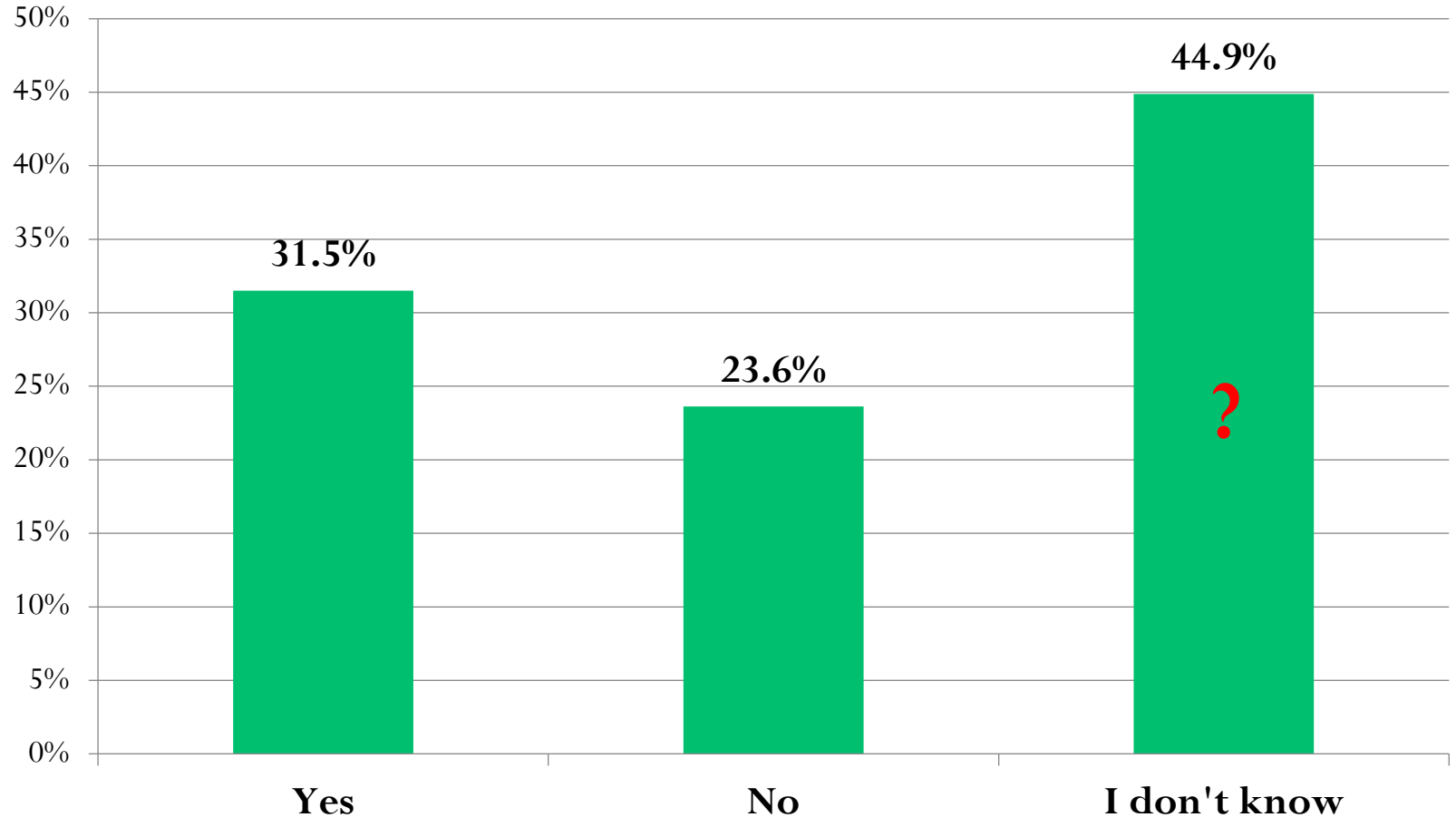
What is COVID-induced depression?

- Depressed patients have higher levels of inflammatory markers such as peripheral cytokines and chemokine, acute phase protein (PCR), and inflammatory blood count ratios.
  - COVID-19 infections may trigger chronic inflammation, reduce 5-HT neurotransmission, and cause depressive symptomatology.
- In an open label study, Mazza and colleagues (2022) found that the antidepressant response rate was 89% in patients with a previous history of MDD and 95% in patients without a previous psychiatric history.
  - Mazza and colleagues (2022) speculated that the potentiation of 5-HT neurotransmission by SSRI's directly counteracted the detrimental effects of the systemic inflammation that reduces 5-HT.
- These open-label study findings suggest that the antidepressant response for MDD triggered by COVID-19 infection may differ from the less robust response generally seen in subjects with a more conventional depressive illness.
  - ***Can COVID-19 induced depression data be merged with non-COVID related data?***

Mazza et al., Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. *Eur Neuropsychopharmacol*. 2022; 54:1-6.

ISCTM Survey Results:

Can the data obtained from subjects with COVID- and non-COVID related mood or anxiety disorders be merged into the same clinical data set?



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Are critical world events confounding factors for clinical trials?

Clearly, some critical world events can affect how we conduct and how we interpret the results of clinical trials

There are some unanswered questions:

- *Is there a different trajectory of illness and treatment response between COVID- and non-COVID related psychiatric disorder?*
  - The same question applies to psychiatric disorders associated with exposure to trauma (e.g., war)
- *Can the data from subjects exposed to critical world events be included in the same study dataset as non-exposed subjects?*