EFFECTS OF NEW ANTIDEPRESSANT PHARMACOTHERAPIES ON SUICIDAL IDEATION AND BEHAVIOR

Specific Aim – We propose to use real-world data from seven integrated health systems to rapidly evaluate the effects of anticipated new antidepressant pharmacotherapies on suicidal ideation and behavior.

Background – Studies with short-term follow-up consistently find that ketamine infusion rapidly reduces suicidal ideation, suggesting that glutamate receptor modulators could reduce suicidal ideation and behavior in people with depressive disorders. The first of those anticipated new pharmacotherapies (Esketamine) has received “breakthrough” designation from the FDA and will likely receive approval (for the indication of treatment-resistant depression) within the next 12 months. Several similar ketamine-class drugs are expected to receive approval over the next few years. Patients, clinicians, and health systems will be intensely interested in the potential benefits of these new drugs (especially regarding reduction of suicide risk) as well as potential adverse effects (including potential for abuse and dependence). Rapid access and assessment of data on benefits and harms data of esketamine in real-world clinical practices across multiple health systems will be essential to addressing these high-priority questions.

Preliminary Studies – The proposed work will build on several areas of existing MHRN infrastructure and investigator expertise, including:

* A well-characterized data infrastructure across all sites, including harmonized representation of member demographics, outpatient and inpatient health service use, prescription medication orders and fills, and patient reported outcomes (including measures of depression severity and suicidal ideation)
* Methods and tools for identifying new episodes of depression treatment (both medication and psychotherapy) and characterizing dose and duration of treatment exposure.
* Methods and tools for ascertaining suicidal ideation, non-fatal suicide attempts, and suicide deaths
* Machine-learning derived models for accurately predicting short-term risk of suicidal behavior
* Expertise in other statistical methods, including methods for identifying/evaluating personalized treatment strategies, selecting variables for inclusion in propensity score models, and multiple sequential testing for medication safety surveillance

Design and Methods – Using data from seven MHRN health systems, we propose to:

* Identify new episodes of treatment with Esketamine and other new glutamate receptor modulator drugs
* Characterize prior treatment history and pre-treatment prognostic characteristics in this group
* Use variable selection methods to develop prognostic scores and propensity scores for treatment selection
* Investigate alternative methods for unbiased estimation of treatment effects, including:
  + Identifying a propensity-score matched comparison group of comparable patients treated with alternative second- and third-line depression treatments
  + Including a larger cohort of control patients to preserve power, and using high-dimensional propensity score models to analytically control for potential confounders
* Compare outcomes of suicidal ideation and suicidal behavior (suicide attempt or death), accounting for baseline prognostic characteristics.

Innovation and Impact – This work will provide much-needed early data regarding benefits and possible adverse effects of potential breakthrough treatments for depression and suicide risk. This work builds on essential data infrastructure and analytic methods developed in previous MHRN research, and is likely only possible in our network because we have the infrastructure and sample size needed to conduct the analyses. This work will both support and benefit from the parallel development of the proposed new MHRN Methods Core.

Lead Investigator – Susan Shortreed

Sites Interested – KPWA, KPCO, KPHI, HFHS, HealthPartners, KPNW, KPSC

Work Plan:

* Lead site (KPWA) will develop distributed programs to create analytic datasets from VDW and Clarity sources
* Sites will share de-identified (per HIPAA) datasets for centralized analysis
* KPWA team will lead design and conduct of analyses
* Investigators from all sites will participate in interpretation and preparation of manuscripts

Timeline and budget scheme – Given expectations for the approval and uptake of new treatments, this project should begin no sooner than year 3 of the anticipated next MHRN funding cycle (approximately June 2021).

Anticipated total budget (including F&A costs) will be approximately $210,000 for the KPWA site and approximately $65,000 for other sites – for a total budget of approximately $600,000. This would likely be divided across two project budget years.