A Flexible Home-Based Transdermal Flumazenil Protocol for PAWS (Post-Acute Withdrawal Syndrome) / BIND (Benzodiazepine-Induced Neurological Dysfunction)

ABSTRACT

Background: Benzodiazepine-induced neurological dysfunction (BIND) and post-acute withdrawal syndrome (PAWS) affect an estimated 10–25% of long-term benzodiazepine users, the majority of whom acquired their dependence iatrogenically. Despite decades of evidence supporting flumazenil as an effective treatment, no standardized protocol exists, and all published approaches share a critical limitation: treatment windows that are too short, too costly, and too dependent on inpatient infrastructure to be widely accessible.

Objectives: This study aims to evaluate the safety, tolerability, and clinical effectiveness of a patient-directed, flexible-dose transdermal flumazenil protocol administered at home under remote clinical supervision. Secondary objectives include characterizing the effective dose range, assessing functional recovery, and establishing a replicable multicenter framework.

Hypotheses: Hypothesis 1: Self-applied transdermal flumazenil can achieve sufficient systemic absorption to serve as a clinically effective alternative to intravenous or subcutaneous administration. **Hypothesis 2:** Given the profound heterogeneity of PAWS/BIND in both duration and severity, ranging from months to years and from mild impairment to complete debilitation requiring around-the-clock care, a patient-directed home-based dosing approach is well-suited to this population, and the effective dose is expected to vary substantially between individuals.

Methods: Adults fully discontinued from benzodiazepines for a minimum of 30 days and presenting with persistent PAWS/BIND symptoms will be enrolled following an initial in-person evaluation. Flumazenil compounded in a transdermal cream will be applied 4 to 6 times daily. Dose escalation begins at 1 mg per application and advances in 1 mg increments at the patient's direction, up to a maximum of 24 mg per day. A therapeutic hold phase of a minimum of 3 weeks is observed at the effective dose before gradual de-escalation. Weekly telehealth check-ins provide ongoing clinical supervision throughout. Outcome measures include the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), the SF-36 Quality of Life scale, and a structured functional outcomes checklist.

Expected Contribution: This protocol addresses the single most cited gap in the flumazenil literature: treatment duration. By removing arbitrary time ceilings and allowing therapy to continue for as long as the patient's nervous system requires, its home-based, low-cost design makes it broadly accessible and suitable for multicenter adoption without specialized infrastructure.