# Getting SMART for Pediatric Epilepsy

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Study Protocol and Statistical Analysis Plan

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Sleep disturbances are more prevalent in children with epilepsy whose sleep can be disrupted by seizures occurring during the night and/or during the day. Melatonin is a naturally occurring hormone produced in the pineal which regulates sleep-wake cycles and facilitates quality sleep. Therefore, the purpose of this study is to evaluate the effect of melatonin for improving sleep and seizure control in children and adolescents with epilepsy.

This single-center, randomized, placebo-controlled crossover study was conducted at the pediatric neurologic clinic of National Taiwan University Hospital (NTUH), a tertiary care center in northern Taiwan. The study protocol was approved by the NTUH institutional review board. Written informed consent was obtained from parents, and assent was obtained from participants where appropriate. The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Eligible participants were children aged 1 to 18 years with a confirmed diagnosis of epilepsy and with sleep problems. Exclusion criteria included: (1) children who are bedridden with limited mobility; (2) children with liver or kidney dysfunction; (3) children on hypnotics, antidepressants, or anxiolytics within 4 weeks before the baseline clinic visit; (4) adolescent girls who are pregnant or breastfeeding; and (5) adolescent girls who have sexual activities but cannot take effective contraceptive measures during the trial.

Participants first underwent a 2-week prescreening period, during which they received behavioral and educational interventions targeting sleep health. They were instructed to follow a consistent sleep schedule and adhere to proper sleep hygiene practices. The prescreening period served as an opportunity to identify children whose sleep problems could be effectively managed with non-pharmacological behavioral interventions, ensuring that only those requiring additional treatment were randomized. Following prescreening, participants were randomized to receive either oral melatonin (2 mg/d for children younger than 6 years or 4 mg/d for those 6 years and older) or

placebo once daily after dinner, 1 to 2 hours before bedtime for 4 weeks. Following a 2-week washout period, participants crossed over to the alternate treatment. The study medication was administered as an adjunct to participants' existing epilepsy treatments, which maintained unchanged throughout the study. Study assessments were conducted at the beginning and end of each treatment period. These included actigraphy sleep recordings, seizure assessments, completion of study questionnaires, documentation of adverse events, collection of blood and urine samples, and adherence monitoring through pill counts.

Analyses followed a modified intention-to-treat approach, excluding participants who withdrew before treatment allocation. Baseline participant characteristics were compared between treatment groups using independent-sample t-tests for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables. Given the crossover design, generalized estimating equations (GEE) with an unstructured working correlation matrix and robust standard error estimates were used to assess treatment effects and carryover effects on study outcomes adjusted for age and sex as covariates. Sensitivity analyses were conducted using paired-sample t-tests to compare within-subject differences in outcomes before and after treatment between the melatonin and placebo conditions. Statistical analyses were conducted using Statistical Program for Social Sciences Version 22.0 (SPSS™, IBM Inc., Armonk, NY, USA). All tests were two-sided at $\alpha = .05$.