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A pilot study of actigraphy as an objective measure of SSRI activation symptoms; results from a randomized placebo controlled psychopharmacological treatment study

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) are an efficacious and effective treatment for pediatric obsessive-compulsive disorder (OCD) but have received scrutiny due to a potential side effect constellation called activation syndrome. While recent research introduced a subjective measure of activation syndrome, objective measures have not been tested. This pilot study, using data from a larger randomized-controlled trial, investigated the potential of actigraphy to provide an objective measure of activation symptoms in 44 youths with OCD beginning an SSRI medication regimen. Data were collected over the first four weeks of a multisite, parallel, double-blind, randomized, placebo controlled psychopharmacological treatment study and statistical modeling was utilized to test how activation syndrome severity predicts daily and nightly activity

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levels. Results indicated that youths with higher activation symptoms had lower daytime activity levels when treatment averages were analyzed; in contrast youths who experienced onset of activation symptoms one week were more likely to have higher daytime and night-time activity ratings that week. Results support actigraphy as a potential objective measure of activation symptoms. Subsequent studies are needed to confirm these findings and test clinical applications for use by clinicians to monitor activation syndrome during SSRI treatment. National Institutes of Health (5U01 MH078594-01); NCT00382291.

Keywords

Selective serotonin reuptake inhibitors; Obsessive-compulsive disorder; Children; Treatment; Activation syndrome; Randomized-controlled trial

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have been linked to the development of a distinct constellation of behavioral side effects, variably referred to as “Behavioral Activation”, “Activation Syndrome”, and “Antidepressant-Induced Jitteriness/Anxiety Syndrome” (Dimidjian et al., 2006; Harada, Sakamoto, and Ishigooka, 2008; Sinclair et al., 2009). The varying terminology likely reflects the heterogeneous presentation of these SSRI-linked adverse events and to date, no strict diagnostic criteria have been defined for activation syndrome. The U.S. Food and Drug Administration (FDA) described a symptom set consisting of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania that might be linked to worsening depression and suicidal ideation development (FDA, 2010). Reid et al. (2010) proposed organizing the most common activation symptoms into five symptom clusters (i.e., irritability, akathisia, disinhibition, mania, and self-harm) and, in combination with work by Bussing and colleagues (2013), psychometrically validated the first dimensional parent-report measure for activation symptoms called the Treatment Emergent Activation Syndrome Assessment Profile (TEASAP). The TEASAP uniquely measures these symptom clusters, producing five subscale scores and an overall activation score.

To enhance research into the phenomenology and etiology of activation syndrome, additional objective and clinically feasible measurement approaches are needed. Since restlessness, behavioral disinhibition and increased energy are all associated with activation syndrome (Sinclair et al., 2009), actigraphy may be a plausible assessment tool warranting further investigation. Actigraphy involves participants wearing a wrist-like device that tracks light and movement, providing accurate feedback regarding activity levels over extended time periods. Actigraphy devices have strong psychometric support (Berlin, Storti, and Brach, 2006) and extensive use in sleep disorder (Sadeh and Acebo, 2002), attention-deficit hyperactivity disorder (De Crescenzo et al., 2014) and depressive disorder research (Burton et al., 2012). Preliminary research has employed actigraphy in research addressing sleep in anxiety disorders (e.g., Alfano and Kim, 2011; Drummond et al., 2012) and developmental disorders (e.g., Tyron et al., 2006).

A large literature links higher depressive symptoms to lower activity levels (e.g., Jacka et al., 2011; Mangerud et al., 2014). Notably, 60% of children and adolescents with depressive disorders have low activity compared to 40% of those with anxiety disorders (Mangerud et al., 2014). To the best of the authors' knowledge, activity levels in pediatric OCD have never been reported and little theoretical research has even postulated an association between obsessive-compulsive symptoms and activity (Abrantes et al., 2012; Albert et al., 2013). Therefore, studying the association between activation and actigraphy in an OCD sample (compared to a depressive disorder sample) may allow for a less biased analysis than a depressive disorder sample because findings would be less clouded by the impact of primary psychopathology on activity.

The goal of this pilot study was to investigate the utility of actigraphy to capture symptoms of activation syndrome in youths beginning an SSRI regimen to treat obsessive-compulsive symptoms. The two aims of this study are to: (1) document if actigraphy is sensitive to average changes in activation symptoms across treatment, and (2) examine week-to-week fluctuations in activation symptoms. Based on the review above, it is hypothesized that emerging symptoms of activation syndrome on the TEASAP will predict higher activity levels. Data analyzed in this study come from a larger randomized-controlled trial.

2. Methods

2.1 Participants and procedures

Participants consisted of 56 treatment seeking youths recruited between February 2009 and January 2011 that enrolled in a double-blind randomized controlled study conducted at two large southeastern university clinics. Institutional Review Boards approved the study at both site locations and parental consent and child assent was acquired for all subjects.

Participants were recruited until sample size goals were obtained. Forty-four (79%) of the 56 participants (25 at site 1, 19 at site 2) consented to wear an actigraphy device during the first four weeks of study participation and produced usable data. These participants consisted of 21 (48%) females; 43 (98%) identified as Caucasian and one (2%) identified as Hispanic. The average participant age was 11.8 years ($SD = 3.3$ years; range 7–17 years). For a more detailed description of baseline characteristics specific to each randomization group, please refer to Table 1.

At the screening visit, study eligibility was determined and those eligible for inclusion were instructed to wear the actigraphy device starting one week before their next visit, the baseline visit. Eligible children and adolescents met criteria for OCD of at least moderate clinical severity (as reflected in Children's Yale-Brown Obsessive-Compulsive Scale total score ≥ 18 ; Scahill et al., 1997). Children and adolescents meeting criteria for substance abuse, bipolar disorder, autism, schizophrenia, mental retardation or chronic degenerative neurological disease were excluded. Participants were excluded if they were taking any other psychopharmacological medication with the exception of stimulants and PRN sedative/hypnotics for insomnia. Diagnoses were consistent with the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (American Psychiatric Association, 2000) and were ascertained through clinical interview and a semi-structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children; Kaufman et

al., 1997). In addition to OCD, seven (16%) participants met diagnostic criteria for comorbid ADHD; 25 (57%) for a comorbid anxiety disorder, seven (16%) for a comorbid tic disorder, two (5%) for comorbid depressive disorder and eight (18%) for other disorders (i.e., elimination disorders, oppositional defiant disorder and phonological disorder). Altogether eight (20%) participants met criteria for an OCD diagnosis and no comorbid diagnoses, 20 (46%) for one comorbid diagnosis, and 10 (23%) for two or more comorbid diagnoses. Please refer to Figure 1 for a study flow chart.

At baseline, participants were randomized in a parallel design to one of three medication arms: regular sertraline titration, slow sertraline titration or placebo (1:1:1 allocation; computer generated randomization sequence stratified by age (7–12 year old and 13–17 year old groups). All participants and study investigators/clinicians remained blind until the conclusion of treatment; assignment of participants to intervention group was conducted by one unblinded study nurse not involved in assessments. The primary aim of the randomized-controlled trial was to investigate impact of titration speed on activation symptom presentation. The current study displays findings for a secondary outcome of interest from the trial related to the ability of actigraphy to objectively measure symptoms of activation syndrome. To investigate this research aim, participants were closely monitored for symptoms suggestive of activation syndrome for one week prior to randomization and during the first three weekly follow-up visits of the randomized-controlled trial. Actigraphy devices were worn and sleep diaries were completed during these four weeks. This time period did not include any exposure to cognitive behavioral therapy, which was initiated at week 4.

2.2 Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL)—The K-SADS-PL (Kaufman et al., 1997) is an adapted version of the K-SADS, a parent-child interview measure used to diagnose several childhood psychiatric disorders and their severity. The K-SADS-PL extends upon previous versions as it includes several new disorders (attention-deficit hyperactivity disorder, posttraumatic stress disorder, and tic disorders), assesses global functioning, and includes both lifetime and current psychopathology. In addition to the disorders already mentioned, the K-SADS-PL assesses depressive disorders, bipolar disorder, anxiety disorders, conduct disorder, and oppositional defiant disorder. The K-SADS-PL has high test-retest reliability, inter-rater reliability, as well as strong agreement with other diagnostic instruments used to assess specific disorders (Kaufman et al., 1997).

Sleep Diary—The sleep diary is a brief self-report log of sleep habits that combined with actigraphy data, is the gold standard for measuring sleep (Espie, 2000; Wolfson et al., 2003; Buysse et al., 2006). The sleep diary was completed daily from screening through the end-of-week-3 visit upon awakening and required approximately 3 minutes/day to complete (Lichstein, Riedel, and Means 1999).

Actigraphy—Participants wore wrist-band style Mini Mitter Actical® actigraphy devices (Starr Life Sciences Corp., USA) on their non-dominant wrist daily for 4 weeks starting at

the baseline visit. The device detects frequency and intensity of motion and has been shown to be valid and reliable for recording general activity levels (Chang et al., 1999; Swanson et al., 2002) and SSRI related motor activity (Putzhammer et al., 2005). The study reports average activity units, converted to a rate per minute of real time, for day and night-time periods.

Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP)

—The TEASAP (Bussing et al., 2013) is a parent-rated assessment of activation symptom severity that captures five identified symptom clusters related to Activation Syndrome: (1) Irritability (9 items), (2) Akathisia/Hyperkinesia/Somatic Anxiety (6 items), (3) Disinhibition/Impulsivity (7 items), (4) Mania (10 items), and (5) Self-injury/Suicidality/Harm to others (6 items). Parents rate the child's behavior in the past week, considering frequency and impairment associated with the behavior on a 4-point Likert-style scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe). The five subscales are summed to create a Total Score of activation symptom severity used for all analyses in this study. The TEASAP has strong psychometric properties, including the ability to capture week-to-week fluctuation in activation symptom severity (Bussing et al., 2013).

2.3 Statistical analyses

All data were checked for accuracy and all statistical analyses were conducted using the Statistical Package for the Social Sciences version 20.0 (IBM, Armonk, NY, USA). Descriptive statistics, including checks of General Linear Model sample assumptions, were calculated to ensure the appropriateness of statistical analyses utilized. Covariates were identified based off previous literature or the study methodology utilized (e.g., site differences). Body mass index was not included as a covariate due to the limited variability observed in this sample (BMI at Screening: Mean: 20.36, Standard Deviation: 4.30; max was 2 participants who were “moderately obese”) and inherent multicollinearity with the weight-adjusted sertraline dosage level used as a covariate for all activity related analyses.

In accordance with traditional guidelines for assessing sleep, both objective (i.e., actigraphy) and subjective (i.e., sleep diaries) measures were used to determine the child's day and night-time periods (Espie, 2000). Weighted averages of activity levels for these day and nighttime periods were calculated; weighting was based off the number of hours of activity that were recorded. Day and night periods were defined as the time listed on the sleep diary where the participant attempted to fall asleep (rounded down to nearest hour) and where they woke up for the final time (rounded up to the nearest hour). If subjects had not worn the device for three or more consecutive hours we excluded this day or nighttime period from all analyses. A description of missing data quantities and reasons for missing data is provided below.

Multilevel modeling (MLM; Singer and Willett, 2003) was utilized to analyze longitudinal data because 1) it offers simultaneous measurement of intra-individual (referred to as *Fixed Effects*) and inter-individual (referred to as *Random Effects*) variability in study measures (Singer and Willett, 2003); 2) it allows tailoring the *Repeated Measures* (relation of dependent variable to itself over time) and *Random Error Structures* (relationship between

intercept and slope over time) (Singer and Willett, 2003); and 3) statistical power is not significantly hindered by missing data (Burr and Nesselroade, 1990; Willett 1990). While a consistent “rule of thumb” for appropriate sample size in MLM has been debated in the literature, Snijders and Bosker (1999) suggest a minimum sample size of 30 participants or more as “large.” Thus, it was determined that a sample of 30 participants would be powered to investigate the aims of this study.

For the results below, two separate MLM analyses were calculated with daytime and nighttime activity levels as the two dependent variables. For each analysis, covariates of age (Model A), gender (Model B), site location (Model C), and average weight-adjusted drug dosage (Model D), and then the independent variable of parent rated activation symptoms (Model E). Group randomization was inherently controlled for by the inclusion of Model D. All models were nested to allow for direct comparison and were dropped from all subsequent analyses if they did not significantly improve upon the previous model. This was determined by a chi-squared test of the reduction in the $-2 \text{ Log Likelihood}$ ($-2LL$) and visual inspection of the *Bayesian information criterion* (BIC). This information for the analysis with daytime activity levels can be observed in Table 1.

3. Results

3.1 Preliminary analyses

Missing data for parental-rated activation was 9% during the four weeks of data collection. Missing data for daytime activity was 35% and 20% for nighttime activity levels over the four weeks of data collected. Missing data resulted from patient’s missing a session, failing to complete a study measure at an appointment or at home (i.e., sleep diary), or if a participant failed to wear their actigraphy device enough to meet the daily inclusionary criteria (see methods). Descriptive data and checks for normality for each study measure were calculated for each data collection time point. MLM operates under the assumptions of the *General Linear Model* and thus a 90% Winsorisation procedure was utilized for any study dependent variable, specifically night time activity, with non-normal data (Guttman, 1973). No independent variables had non-normality. Please refer to Table 2 for descriptive data of the study variables over the course of the treatment period analyzed.

Echoing similar analyses reported by Bussing and colleagues (2013), number of comorbidities was not significantly associated with TEASAP ratings ($0.11, p = 0.25$) in the entire sample. A higher number of comorbidities was weakly associated with higher daytime activity levels ($0.35, p < 0.05$), but not night-time activity levels ($-0.01, p = 0.97$), which aligned findings that showed that number of comorbidities had no association with any sleep variables. The pattern of significance of these findings did not differ based on randomization group. Taken together, number of comorbidities was not originally included as a covariate. Post-hoc analyses confirmed that inclusion of comorbidity status did not alter the association between activation and activity level reported below.

3.2. Longitudinal associations with daytime activity levels

Age (Model A), gender (Model B), and SSRI drug dosage (Model D) all were identified to have at least a marginally significant relation to daytime activity levels. At a trend level,

increasing age predicted a decrease in average daytime activity levels across treatment ($-31.85, p < 0.08$). There was a significant association between gender and daytime activity levels, where being female related to a decrease in daytime activity levels ($-213.52, p < 0.05$). At a trend level, higher SSRI dosage was associated with lower average activity level across the four weeks ($-90.45, p < 0.08$). Site differences were non-significant and failed to meet criteria for inclusion in the final analyses.

Parent rated activation (Model E) significantly predicted both average and weekly fluctuations in daytime activity levels. The parent rated activation model (Model E) significantly improved upon the covariate models A–D ($\chi^2 (7, N = 37) = 267.60, p < 0.001$) and resulted in a large reduction in the BIC. Average parent rated activation significantly predicted average daytime activity levels, where a one standard deviation increase in parent rated activation predicted a 6.320 decrease in average activity levels ($p < 0.05$). This predictor explained an additional 17.7% of the *Fixed Effect* variance in daytime activity levels. A larger effect was observed for week-to-week fluctuations in parent rated activation. A one standard deviation increase in parent rated activation from the previous week predicted a 273.07 increase in daytime activity from the previous week ($p < 0.05$). The standard deviation for average change from the previous week in daytime activity was 335.86; therefore a 273.07 increase represents a 0.81 standard deviation change (large effect size). A pseudo R^2 indicated that this version of Model E explained 87% of the *Random Effects* variance remaining after Model D.

3.3. Longitudinal associations with night-time activity levels

The MLM for daytime activity was replicated with nighttime activity as the dependent variable. Unlike for daytime activity, age was not associated with average nighttime activity ($0.53, p = 0.91$). When Model A was entered there was insignificant variability in average nighttime activity levels to allow for further *Fixed Effects* analysis. Thus, Models B through D were not entered as they only contain *Fixed Effects* predictors and only the *Random Effect* predictor from Model E (week-to-week fluctuations in activation) was entered after Model A. This version of Model E significantly improved upon Model A. Results found that a one standard deviation increase in parent rated activation from the previous week predicted a 19.338 increase in nighttime activity from the previous week ($p < 0.05$). The standard deviation for average change from the previous week in nighttime activity was 11.66, therefore a 19.34 increase represents approximately a 1.66 standard deviation change (large effect size). Indeed, a pseudo R^2 indicated that this version of Model E explained 88% of the *Random Effects* variance remaining after Model A.

4. Discussion

In this pilot study, weekly changes in parental ratings of symptoms of activation syndrome corresponded with weekly changes in objective measurements of activity during day and night time. This finding supports the conjecture that activation syndrome onset includes an immediate physical component of heightened activity, in addition to mental and emotional changes, and suggests that actigraphy could be an appropriate assessment tool of this activity increase. Higher average levels of activation syndrome predicted lower average levels of daytime activity during the first four weeks of psychopharmacological treatment.

This is the opposite of the association observed when analyzing week-to-week changes. It is plausible that levels of psychopathology, such as obsessive-compulsive or depressive symptoms, are confounding this association since higher anxiety or depression would cause lower activity levels (i.e., more avoidant or less energy) and would spur with higher doses of an SSRI. Future research with longer monitoring periods should attempt to replicate this study and test various confounders or mediators, such as severity of psychopathology, as they may explain these results. Since parental TEASAP ratings predicted night time activity levels, our findings suggest that activation syndrome contains elements of sleep disturbance (i.e., night-time awakenings). This finding that has been inconsistently reported in the literature. Older studies support conceptualizing sleep disturbance as a symptom of activation (e.g., Riddle et al., 1991), while more recent research has found less support (e.g., Reinblatt et al., 2009). Presently insomnia or sleep disturbance is not one of the TEASAP subscales, and only one the 38 TEASAP items directly inquires about sleep (Item 30, decreased need for sleep). The current pilot study findings suggest directing further inquiry to the phenomenon of sleep disturbance in the development of activation syndrome.

The trend level finding that SSRI drug levels were inversely associated with activity levels may seem to contradict the notion that activation syndrome can result from SSRI treatment. However, our finding likely reflects aspects of our double-blind randomized flexible dosing study protocol, namely, 1) clinicians determined whether or not to implement scheduled dosing increases based on assessment of patient's tolerance of current dose; and 2) if clinicians suspected development of activation syndrome, further medication dosing depended on the severity of activation, invoking a treatment algorithm that could include halting dose increase, decreasing doses, or terminating patient from study. Thus, increasing activation scores would have resulted in stagnant or reduced drug doses per protocol.

The clinical implications of these findings extend to any situation where SSRIs are prescribed to pediatric populations and activation syndrome is possible. For example, SSRI treatment of depressive symptoms would benefit from a clinically feasible, objective measure of activation syndrome, especially since activation syndrome may increase the risk of suicidality in these patients (Dopheide, 2006). Furthermore, the clinicians can use the actigraphy devices in other clinically relevant ways. For example, sleep disturbance is frequently reported during treatment of pediatric OCD and hypothesized to be a maintaining factor of obsessive-compulsive symptoms (Storch et al., 2008; Alfano and Kim, 2011). In this situation, actigraphy could simultaneously monitor sleep disturbance and activity levels. Furthermore, emerging research proposes that activity based interventions may be a novel approach to treat refractory OCD (Abrantes et al., 2012). If results are positive, actigraphy devices would be a non-invasive, psychometrically sound method to monitor activity levels.

As with all research, this pilot study has several limitations. First, the prospective relationship between activity levels and symptoms of activation syndrome was only investigated during the first 3 weeks after starting sertraline; thus, future research should investigate these relationships over the full course of SSRI pharmacotherapy for more precise and generalizable results. Second, due to limited sample size, the study lacked power to investigate specific symptom clusters of activation syndrome. Additionally, it is unknown if these results would generalize to other pediatric samples with disorders other than OCD.

However, there are several strengths of this research. This study uses advanced statistical modeling that provides adequate power to conduct this pilot test and investigates an objective measure of activation syndrome which has never been reported in the literature.

Findings indicate that SSRI treatment may be accompanied by changes in activity levels during day and night time, which corresponded to measurement of activation syndrome. Thus, higher physical activity may be harbingers of side effects like activation syndrome. Clinicians should direct attention to assessing activity level and sleep during SSRI initiation. This research also highlights that actigraphy may provide an objective method for clinicians to track weekly changes in activation symptom severity. This pilot study is the first ever to provide support for the ability of actigraphy devices to capture activation syndrome in any clinical population. Thus, the authors believe that in order for actigraphy to begin to be incorporated into clinical practice as a tool to objectively measure activation syndrome, researchers need to 1) replicate this study in a larger clinical sample with multiple clinical presentations and monitor prospective associations over the entire treatment period, 2) further psychometric validation of this clinical tool (e.g., reliability and validity), 3) benchmark activity level changes that suggest clinically relevant changes in activation, and 4) conduct a randomized trial to test if actigraphy devices improve clinical care beyond treatment as usual. Increasing numbers of smart phone applications might serve for even more non-intrusive data collection for actigraphy purposes; this promises to be a fertile field for further study.

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Highlights

- Actigraphy could be an objective measure of activation syndrome in children on SSRIs.
- We model the prospective association of activation syndrome and day/night activity levels.
- Week-to-week increases in activation syndrome were mirrored by increases in activity levels.
- Children who experienced more activation syndrome during treatment had lower activity levels.

Figure 1.

Study Flow Chart

Note: One subject randomized to the slow sertraline titration arm withdrew consent within a week of beginning the trial.

Table 1

Demographic and baseline clinical characteristics of the sample

	RegSert + CBT (<i>n</i> = 14)	SloSert + CBT (<i>n</i> = 17)	PBO + CBT (<i>n</i> = 13)
Gender <i>N</i> (% Female)	50.00	52.90	38.50
Age, <i>M</i> (<i>SD</i>)	11.70 (2.70)	11.24 (3.45)	12.01 (3.86)
CY-BOCS total	23.71 (4.03)	25.71 (4.33)	26.15 (3.67)
Psychiatric comorbidity, <i>N</i> (%)			
Internalizing	7 (50%)	8 (47.01%)	9 (69.23%)
Externalizing	3 (21.4%)	1 (5.88%)	3 (23.07%)
Tic Disorder	3 (21.4%)	2 (11.76%)	3 (23.07%)

Note. CY-BOCS = Children's Yale-Brown Obsessive–Compulsive Scale.

Descriptive data for study variables across study period

Table 2

	TEASAP Score	Dose of Sertraline	Total Activity/24 Hrs	Day- time Activity	Night- time Activity	Sleep Onset	Number of Awakenings	Sleep Efficiency	Time in Bed
<i>Week Before Baseline</i>									
Placebo	–	–	773.63	701.76 (279.54)	71.87 (42.55)	37.25 (40.08)	0.70 (0.40)	0.91 (0.06)	572.64 (104.96)
Slow Titration	–	–	772.65	692.67 (194.27)	79.98 (52.76)	18.41 (10.01)	0.64 (0.83)	0.94 (0.03)	540.37 (107.80)
Regular Titration	–	–	647.95	588.29 (210.20)	59.66 (42.29)	16.91 (8.47)	0.31 (0.30)	0.95 (0.03)	536.85 (87.99)
<i>Week 1</i>									
Placebo	16.07 (10.65)	0.00	663.57	598.66 (223.56)	64.91 (28.53)	13.88 (6.75)	0.75 (0.61)	0.94 (0.03)	545.31 (48.17)
Slow Titration	21.29 (13.52)	25.73 (2.95)	768.49	679.17 (443.50)	89.32 (64.96)	23.84 (14.67)	0.71 (0.53)	0.93 (0.03)	533.70 (66.56)
Regular Titration	28.10 (14.87)	82.32 (7.99)	749.11	656.59 (212.74)	92.52 (63.30)	23.92 (12.65)	0.65 (0.58)	0.92 (0.05)	532.55 (49.95)
<i>Week 2</i>									
Placebo	15.50 (13.17)	0.00	580.34	529.28 (191.74)	51.06 (9.28)	14.65 (5.38)	0.39 (0.31)	0.93 (0.05)	579.45 (51.75)
Slow Titration	16.41 (11.37)	40.75 (12.13)	751.96	660.44 (393.92)	91.52 (61.26)	19.39 (13.40)	0.74 (0.42)	0.92 (0.05)	514.69 (83.12)
Regular Titration	16.04 (11.61)	116.27 (47.57)	700.19	612.07 (207.43)	88.12 (72.17)	23.36 (11.44)	0.50 (0.56)	0.94 (0.03)	529.55 (75.98)
<i>Week 3</i>									
Placebo	14.75 (13.74)	0.00	650.80	585.29 (212.42)	65.51 (36.81)	21.13 (13.23)	0.36 (0.35)	0.93 (0.05)	556.03 (37.73)
Slow Titration	15.29 (14.75)	44.84 (10.20)	920.34	822.92 (327.27)	97.42 (22.85)	16.62 (7.82)	0.81 (0.61)	0.95 (0.02)	508.39 (75.99)
Regular Titration	19.75 (11.05)	147.50 (46.50)	752.80	657.89 (167.98)	94.91 (58.13)	26.44 (19.11)	0.36 (0.46)	0.91 (0.07)	528.79 (45.15)

Note: TEASAP= Treatment Emergent Activation Syndrome Assessment Profile

Table 3**Multi-Level Modeling of Daytime Activity and Activation**

	UMM	Model A	Model B	Model D	Model E
<i>Fixed Effects</i>					
Intercept	62326.2 (16703.7) ***	70944.6 (24362.1) ***	53303.7 (19055.0) ***	49927.3 (16943.3) ***	41073.9 (13547.3) ***
Age		3.9(9.9)	2.5(9.6)	-15.5(14.6)	-31.9(16.1) +
Gender			-269.5(97.6) **	-231.1(93.3) *	-213.5(91.4) *
Drug				-106.3(52.8) *	-90.5(49.3) +
TEASAP					-6.3(2.6) *
<i>Random Effects</i>					
Residual	48819.8 (3227.4) ***	29030.9(6884.7) ***	28847.8 (6745.8) ***	19869.3 (5335.6) ***	464.7 (913.6)
TEASAP					273.1(138.0) *
<i>Fit Statistics</i>					
-2LL	6814.2	930.5	922.6	788.9	521.3
AIC	6820.2	938.5	933.6	800.9	573.3
BIC	6832.8	947.3	946.0	813.3	550.6
Fixed R ²	-	0.0%	24.9%	6.3%	17.7%
Random R ²	-	40.6%	0.6%	31.1%	87.6%

Note

+ $p < .08$ * $p < .05$ ** $p < .01$ *** $p < .001$.

To increase clarity and fit all data, only 1 decimal place was reported for all statistics. Model C (site) was dropped due to poor fit and therefore not included in this graph to increase clarity.

UMM= Unconditional Means Model; -2LL = -2 Log Likelihood; AIC= Akaike Information Criterion; BIC= Bayesian Information Criterion; Psd= Pseudo; TEASAP= Treatment-Emergent Activation and Suicidality Assessment Profile.

Table 4**Multi-Level Modeling of Night Time Activity and Activation**

	UMM	Model A	Model E
<i>Fixed Effects</i>			
Intercept	77.84 (7.93)***	40.16 (33.87)	72.29 (55.84)
Age		2.98 (2.78)	.528 (4.77)
<i>Random Effects</i>			
Residual	2895.97 (173.15)***	3620.27 (274.40)***	438.84 (357.38)
TEASAP			19.34*
<i>Fit Statistics</i>			
-2LL	6581.48	923.77	471.69
AIC	6587.48	933.71	481.69
BIC	6600.68	941.35	490.38
Fixed R ²	–	48.41%	0.00%
Random R ²	–	0.00%	87.88%

Note:

*
 $p < .05$ ***
 $p < .001$.

After Model A, only the Random Effect predictor of Model E was added due to lack of between subject variance.

UMM= Unconditional Means Model; -2LL= -2 Log Likelihood; AIC= Akaike Information Criterion; BIC= Bayesian Information Criterion; Psd= Pseudo; TEASAP= Treatment-Emergent Activation and Suicidality Assessment Profile