SUPPLEMENTAL MATERIAL

Educational Level

The educational level was scored as follows: 1=grade 6 or less; 2=grade 7 to 12; 3=graduated high school; 4=part college; 5=graduated 2 year college; 6=graduated 4 year college; 7=part graduate/professional school; 8=completed graduate/professional school.

Neuropsychological Tests

N-back task: We used the 0-, 1-, 2- and 3-back versions of the N-back task to impose a gradient on working memory load as described in [1]. The N-back is thought to measure the performance of various working memory processes, including maintenance, monitoring, updating and manipulating the remembered information.

Attention Network Test (ANT): This test assesses three different components of attention as described in [2]: (1) the alerting system, which has been associated with the frontal and parietal regions and is thought to be modulated by the central noradrenergic receptor system [3]; (2) the orienting system, which has been associated with areas of the parietal and frontal lobes [4]; (3) the executive control of attention, which often is studied by tasks that involve conflict (e.g., Stroop task), and activates the dorsal medial prefrontal cortex (anterior cingulate) and the lateral prefrontal cortex in fMRI studies [5].

Monetary Incentive Delay (MID) task: The MID task session consisted of 224 trials, each followed by a 6 sec interval. The MID task was applied after Knutson *et al.* [6]: During each trial, participants saw one of seven cue shapes (cue; 250 ms), then fixated on a crosshair as they waited a variable interval (delay; 2000–2500 ms), and then responded to a solid white target square which appeared for a variable length of time (target; 160–330 ms) with a button press. Feedback which followed the target's disappearance with a variable delay of 1450-1850 ms notified participants whether they had won or lost money during that trial and indicated their cumulative total at that point. On incentive trials, volunteers could win or avoid losing

money by pressing the button during target presentation. Task difficulty, based on reaction times collected during the practice trials in each session, was set such that each subject would succeed on approximately 66% of his or her target responses, a rate based upon the conditioned reinforcement rate needed to maintain firing activity of dopamine neurons in monkeys performing similar tasks [7]. Cues signaled potentially rewarding outcomes (96 trials; denoted by outline of circles), potential loss outcomes (96 trials; denoted by outline of squares), or no monetary outcome (32 trials; denoted by outline of triangles). Reward cues signaled the possibility of winning either $0.20 (32 trials; a circle with one horizontal line), $1.00 (32 trials; a circle with two horizontal lines), or $5.00 (32 trials; a circle with three horizontal lines). Similarly, loss cues signaled the possibility of losing either $0.20 (32 trials; a square with one horizontal line), $1.00 (32 trials; a square with two horizontal lines), or $5.00 (32 trials; a square with three horizontal lines). Subjects were informed that they would receive one-third of the money they won during the MID in each session after completion of the study.

Statistical Analysis

Full factorial linear mixed models with restricted maximum likelihood estimation were used to examine the effects of various outcome measures. Schwarz's Bayesian criteria were used to determine the best fitting covariance structure for each set of measures in cases where the typical compound symmetry approach used by ANOVA did not provide the optimal structure for the extant data. The effects of treatment, diagnosis, and time on each behavioral measure were assessed with linear mixed models with a heterogeneous compound symmetry covariance structure. The three ANT measures were examined separately with a similar model including factors for treatment and diagnosis with a diagonal covariance structure. The MID task was analyzed with factors for treatment, diagnosis, and incentive level using a heterogeneous Toeplitz covariance structure. The amount earned included factors for

treatment and diagnosis with a compound symmetry covariance structure. The N-back task data were examined using a model that included treatment, diagnosis and N-back level factors with a first order autoregressive covariance structure.

We did not find an effect of the session order (i.e., whether AMPT or placebo sessions occurred first) on task performance. The relationships between the changes in MADRS scores and the changes in other clinical scales were assessed by computing Pearson correlation coefficients. The relationships between performance differences on the N-back, ANT and MID tasks between the AMPT and placebo conditions also were assessed using correlational analyses. Finally, the correlations between changes in clinical scales and changes in neuropsychological tasks were examined specifically in the RMDD subjects. The significance threshold for these contrasts was set at alpha=0.05, two-tailed, after applying Bonferroni correction for six comparisons (i.e., $p<0.0083$). SPSS 15.0.1 was used for all analyses. Means are reported with their associated standard deviations.

Clinical Ratings

The highest depression ratings were found ~24 hours after the first AMPT dose, when the MADRS and HAMD ratings increased ($p<.005$) in the RMDD sample. By 36 hours, the mean BDI score also had increased significantly in RMDD subjects. In controls, the MADRS and HAMD ratings also increased ($p<.05$) under AMPT versus placebo (Figure 1). Catecholamine depletion was associated with significantly greater increases in depressive symptoms in the RMDD subjects than the controls measured using the MADRS (treatment-by-diagnosis interaction: $F[1,12]=5.86$, $p=0.02$) or the BDI (treatment-by-diagnosis interaction: $F[1,65.0]=4.51$, $p=0.04$). However, the differential AMPT effect measured using the HDRS did not reach significance (treatment-by-diagnosis interaction: $F[1,122]=2.45$, $p=0.12$).

Ratings of anxiety (BAI; p<.05) and akathisia (ADS; p<.01) increased and ratings of pleasure (SHAPS) decreased (p<.001) in the RMDD group under AMPT versus placebo, while the corresponding changes in the controls were not significant (p=0.95, p=0.82 and p=0.76, respectively; Figure 1). The treatment-by-diagnosis interactions assessed by these ratings were significant for pleasure ratings (SHAPS; F[1,39.1]=5.01, p=0.03) but only trended towards significance for anxiety ratings (BAI; F[1,40.4]=3.78, p=0.06) and akathisia ratings (ADS; F[1, 22.9]=3.39, p=0.08). Sleepiness ratings increased in both groups under AMPT versus placebo, but no treatment-by-diagnosis interaction was evident (SSS; F[1,107]=0.78, p=0.38). Hypomanic symptoms increased under AMPT in the RMDD subjects relative to the controls, as reflected by an increase in the mean YMRS score (treatment-by-diagnosis interaction: F[1,114]=7.70, p=0.006) with a peak effect occurring between 48 and 96 hours after initiating AMPT (Figure 2). No clinically significant depressive symptoms were evident between 48 and 96 hours after AMPT in either diagnostic group.

The AMPT-induced changes in the MADRS scores correlated with the corresponding changes in HAMD (r=0.82, p<.001), BAI (r=0.40, p=.03) and SHAPS scores (r=-0.59, p=.001). AMPT-induced changes on YMRS at 96 hours were not correlated with AMPT-induced changes in depression or anxiety ratings at 36 hours. The effects sizes (Cohen's d) for group differences in AMPT-induced symptoms were: MADRS(36h): 1.34, HAMD(36h): 1.20, BDI(36h): 0.62; BAI(36h): 0.58; YMRS(96h): 0.62; SHAPS: 0.87; ADS: 0.80; SSS: 0.44.

In separate models, we excluded 2 RMDD participants with no family history of depression and 5 patients with a family history of alcohol abuse. In each case the drug by group interaction remains significant on the mood response (MADRS), where p=0.002 in both cases. There was no effect of family history of unipolar depression and/or alcohol abuse on the mood response to AMPT within the RMDD group.

N-back Task

Valid N-back task data from both sessions were available for 14 of the 17 RMDD subjects and all 13 controls. No significant effect of AMPT task performance was evident (accuracy: $F[1,82.8]=0.08$, $p=0.78$; reaction time: $F[1,94.4]=0.65$, $p=0.42$; Figure 3). The RMDD subjects and controls did not differ significantly on either performance accuracy ($F[1,41.3]=0.30$, $p=0.59$) or reaction time ($F[1,35.0]=0.47$, $p=0.50$). Pairwise comparisons revealed that there were no effects of drug and diagnosis on any of the 4 difficulty levels. In addition, there was no diagnosis-by-drug-by-difficulty level interaction (accuracy: $F[3,66.3]=1.14$, $p=0.34$; reaction time: $F[3,89.2]=0.52$, $p=0.67$). As expected, N-back task accuracy declined as the delay interval (i.e., the difficulty level) increased ($F[3,50.4]=72.8$, $p<0.001$) although reaction time remained unchanged ($F[3,71.0]=0.08$, $p=0.97$). Psychiatric symptoms as measured with the HDRS, MADRS, BAI, SHAPS and SSS did not correlate with N-back task performance.

ANT

Valid ANT data were available for 16 of the 17 RMDD subjects and all 13 controls. Figure 4 shows the performance as assessed by reaction time differences of correct responses and differences in % correct responses with respect to alertness, orientation and executive attention classified by diagnosis and drug. Based upon differences in reaction time, alertness scores were lower under AMPT than under placebo ($F[1,26.3]=7.58$, $p=0.01$). However, there was no diagnosis-by-drug interaction regarding alertness ($F[1,26.3]=0.41$, $p=0.53$). The main effect of drug and the diagnosis-by-drug interaction on orientation times ($F[1,49.7]=0.17$, $p=0.69$) was not significant. However, the attentional orientation times (difference in reaction time between trials with and without spatial cues) were lower in RMDD subjects than in controls irrespective of treatment condition ($F[1,49.7]=5.10$, $p=0.03$). There was no significant effect of drug or diagnosis on executive attention ($p>.10$).

In RMDD subjects, the AMPT-induced depressive and anxiety symptom ratings were not significantly correlated with changes in attentional performance ($p>0.06$; changes in BAI scores and changes in executive attention tended to be negatively correlated). The AMPT-induced decrease in alertness was not correlated with the AMPT-induced increase in sleepiness as assessed with the SSS scores ($r=0.26$, $p=0.37$).

Differences in performance accuracy as estimated by the changes in percent correct responses with respect to alertness, orientation and executive attention also were examined by diagnosis and drug (Figure 4). There was no significant effect of diagnosis on accuracy scores for the alertness ($F[1,49.2]=0.34$, $p=0.56$), orientation ($F[1,51.6]=3.23$, $p=0.08$), or executive components ($F[1,45.1]=0.07$, $p=0.80$). There also was no significant effect of drug on accuracy of the alertness ($F[1,49.2]=0.56$, $p=0.46$), orientation ($F[1,51.6]=0.33$, $p=0.57$), or executive components ($F[1,45.1]=0.39$, $p=0.54$). Similarly, the interaction of drug and diagnosis had no significant effect on accuracy of the alertness ($F[1,49.2]=0.19$, $p=0.67$), orientation ($F[1,51.6]=0.01$, $p=0.91$) or executive ($F[1,45.1]=0.47$, $p=0.50$) components.

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