Supplemental Information

Methods and Materials

Post Hoc Assessments Based on Changes in MADRS Scores: Although the Montgomery-Asberg Depression Rating Scale (MADRS) ratings were higher in the poor prognosis subjects than the good prognosis subjects (F=5.03, p=0.036), the magnitude of the change in MADRS scores from baseline to study end did not differ significantly between these subgroups (F=0.14, p=0.71). Notably, remission occurred in 9 of 14 cases who did not have an anxiety disorder, but only in 2 of 8 cases with an anxiety disorder (Chi-squared=3.14; p<0.1).

When considering each item of the MADRS independently as a means to determine which items contribute most to the observed antidepressant response, 8 of the 10 items were reduced significantly at the first assessment after the first infusion of scopolamine compared with the item score in the last session before receiving the drug (p<.05). The item regarding sadness (item #2) showed a trend level of reduction (p= 0.09), and the item involving appetite (item #5) was not significant.

Ratings of Acute Mood Changes within Session: The visual analogue scales (VAS) and Profile of Mood State (POMS) ratings indicated that *no acute, within-session changes in emotion ratings occurred during scopolamine* relative to placebo sessions. Thus the drug-by-time interaction was not significant for VAS ratings of happiness, sadness, anxiety, irritation, restlessness or alertness (p>0.15). Similarly, on the POMS the drug-by-time interaction was not significant for the depression (p=0.35), anger (p=0.66) or tension factors (p=0.32). The lack of change in positive mood ratings under scopolamine was consistent with the subjective side effect

reports and the Young Mania Rating Scale (YMRS) results, as no subject experienced euphoria or developed hypomania during the study.

In contrast, changes in the VAS and POMS factors that were sensitive to scopolamine side effects showed clear changes acutely following infusion, which then returned toward the baseline and placebo levels by the final rating within each session (obtained 150 min following initiation of the infusion). Thus, the drug-by-time interaction was significant for the VAS drowsiness rating ($F=7.2$; $p=0.002$; Figure S2A), the POMS vigor factor ($F=7.8$, $p=0.003$; Figure S2B). The fatigue and confusion factors of the POMS also increased at 20 and 60 min post-scopolamine and returned to baseline and placebo levels by session-end, although the drug-by-time interactions showed only nonsignificant trends ($F=2.6$, $p=0.095$ and $F=3.0$, $p=0.065$, respectively; Figure S2 C,D). These changes in the VAS and POMS factor scores appeared compatible with the greater subjective level of sedation experienced under scopolamine.

Effects on Heart Rate and Blood Pressure: The heart rate and blood pressure (BP) decreased under scopolamine versus placebo to an extent that was significant statistically, although no subject developed clinical evidence of hypotension or cardiovascular insufficiency. Thus, while physostigmine was made available at each infusion to allow for rapid reversal of potential scopolamine-induced side effects, no subject developed a medically significant adverse reaction or received physostigmine (i.e., physostigmine administration was neither required nor seriously considered during any session). The main effect of drug was significant for heart rate ($F=22.2$, $p<0.001$; Figure S3), systolic BP ($F=19.5$, $p<0.001$; Figure S4) and diastolic BP ($F=8.6$, $p=0.009$; Figure S5). The drug-by-time interaction was significant for heart rate ($F=7.2$, $p<0.001$), reached trend level for diastolic BP ($F=2.5$, $p=0.08$) and was not significant for systolic BP ($F=1.4$, $p=0.28$).

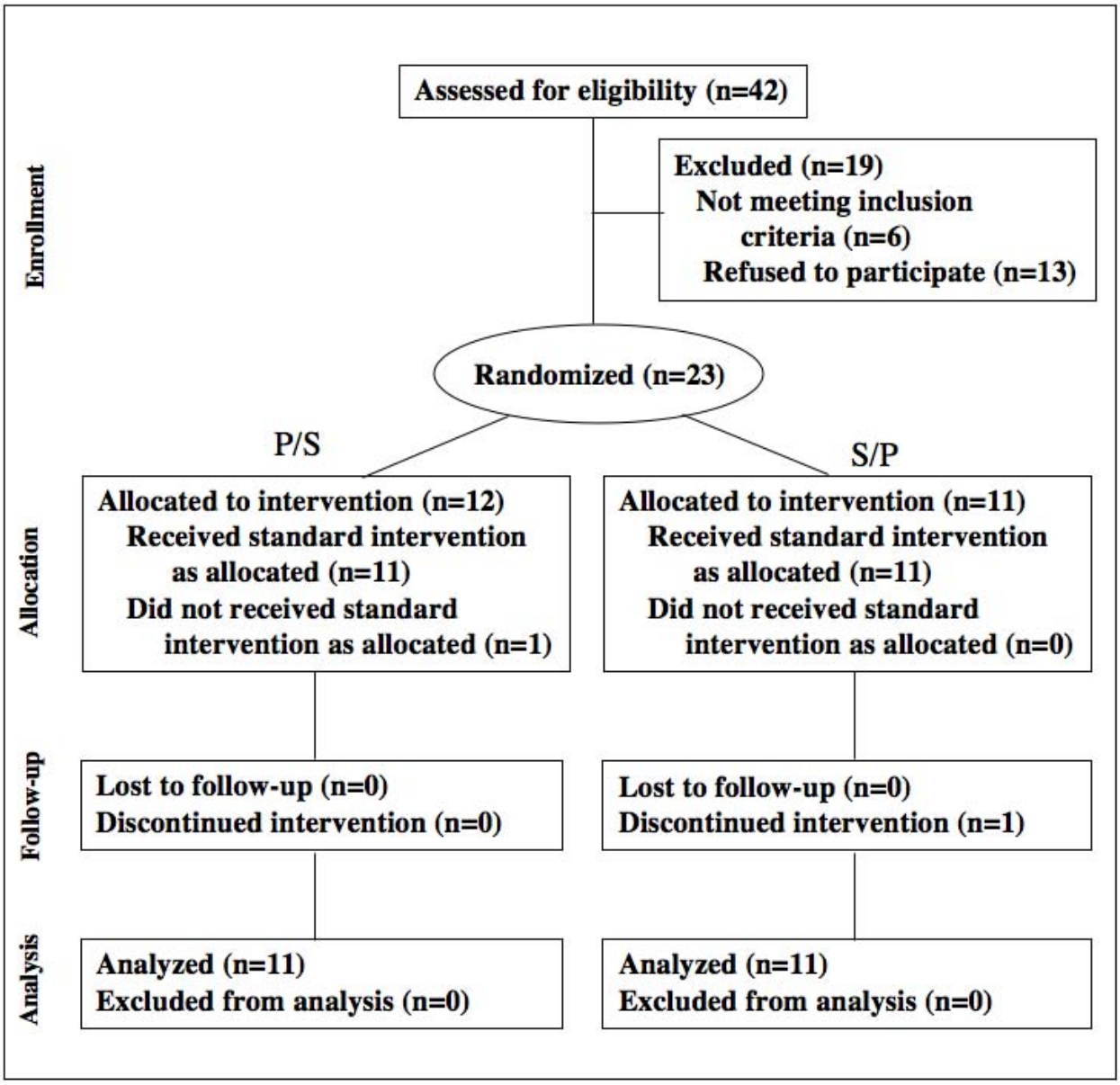

Figure S1. Flow diagram showing patient progress through the study phases. Out-patients were recruited from December, 2005 through March, 2009 at the NIMH. Of 42 eligible patients, 19 were assessed for eligibility but were excluded for not meeting entrance criteria (n=6) or declining to participate (n=13), so 23 were randomized into the study (Figure 2). One subject dropped out after randomization but prior to session 1, so this subject did not contribute any data to the analysis. Twenty-one subjects completed the trial as intended and another subject dropped out after session 6

due to non-response; this subject's data were included in the analysis based upon last observation carried forward (LOCF). Thus a total of 22 patients received the intended treatment and were included in all analyses, 11 of whom were randomized into the P/S group and 11 into the S/P group. In three patients who completed all 7 infusions, the follow-up evaluations could not be obtained for the assessment following session seven (i.e., assessment 8), so analyses were performed using LOCF (from session 7).

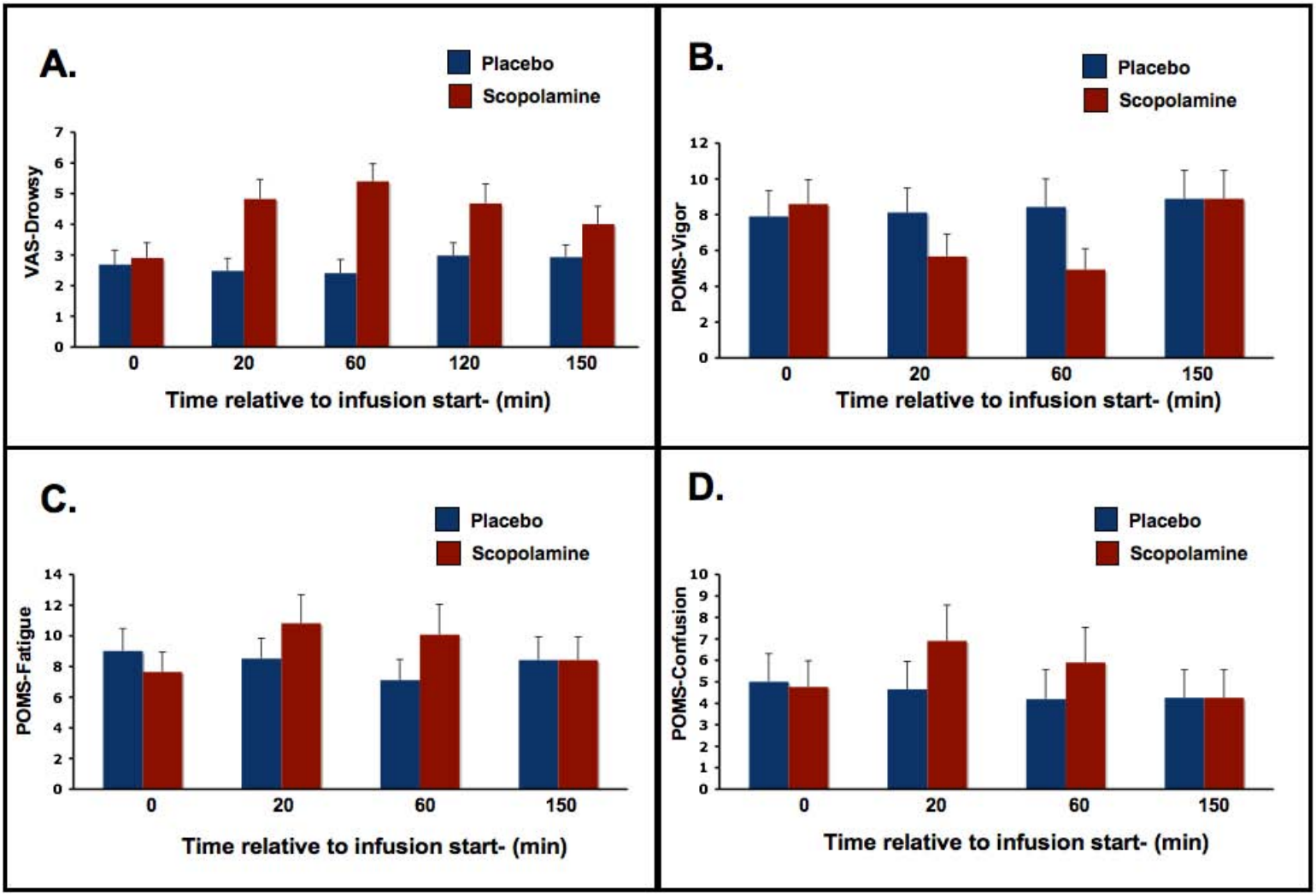

Figure S2. Mean measures (± SE) across placebo (blue) and scopolamine (red) sessions are shown for the VAS-drowsy (A), POMS-vigor (B), POMS-fatigue (C), and POMS-confusion (D) scales.

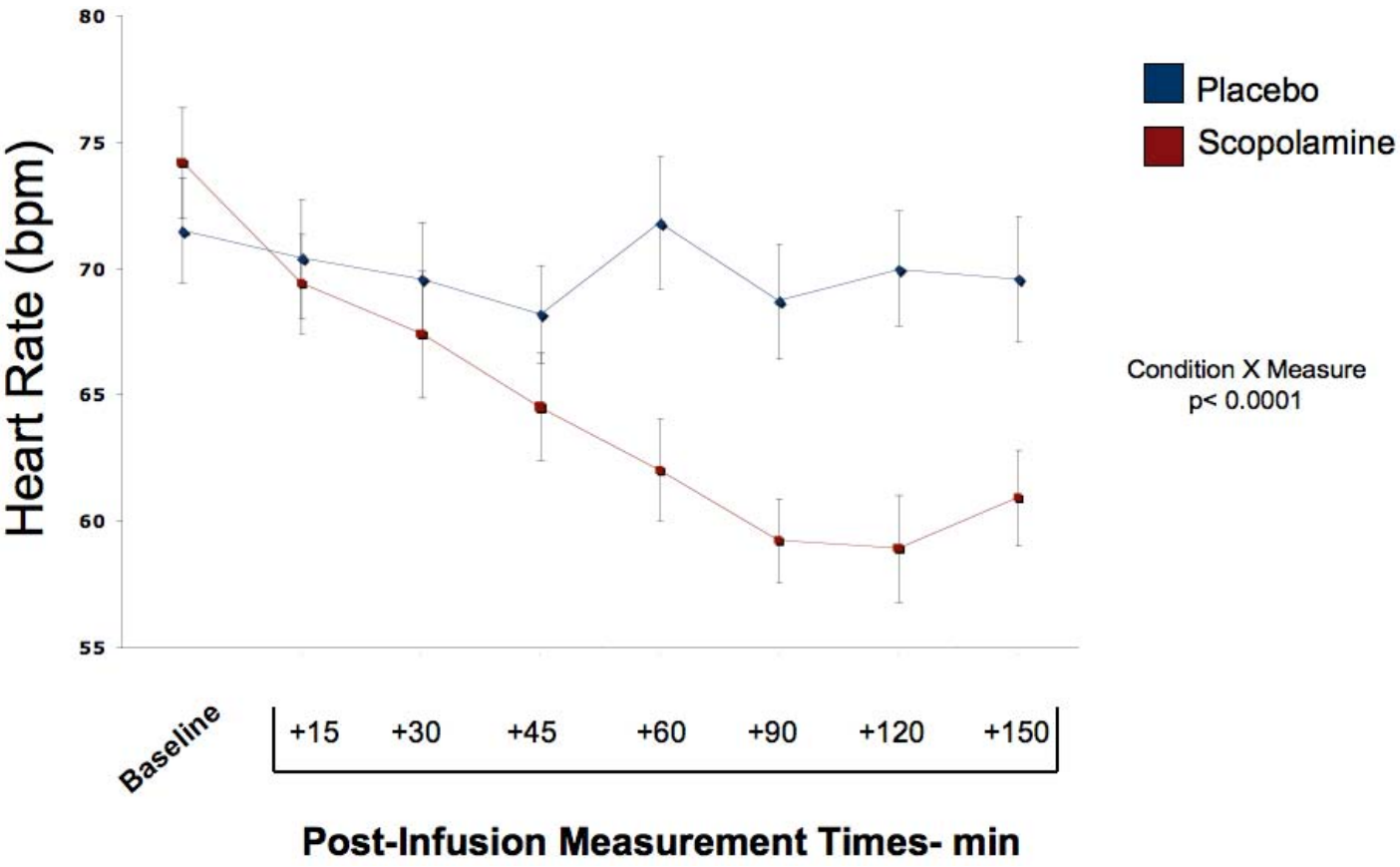

Figure S3. Mean heart rate measures (± SE) across placebo (blue) and scopolamine (red) sessions are shown for time points between baseline and 150 min following the initiation of the infusion.

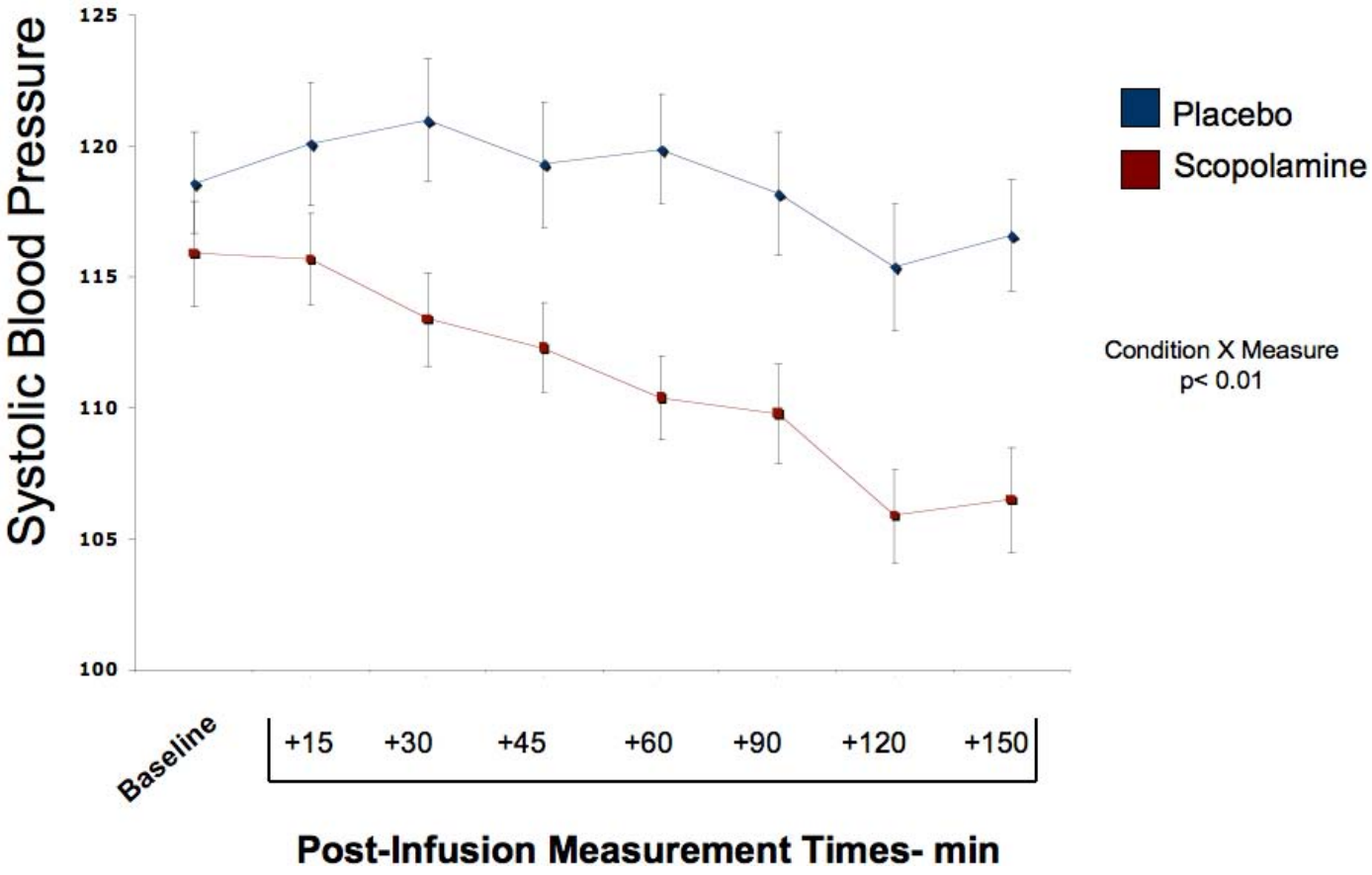

Figure S4. Mean systolic blood pressure measures (± SE) across placebo (blue) and scopolamine (red) sessions are shown for time points between baseline and 150 min following the initiation of the infusion.

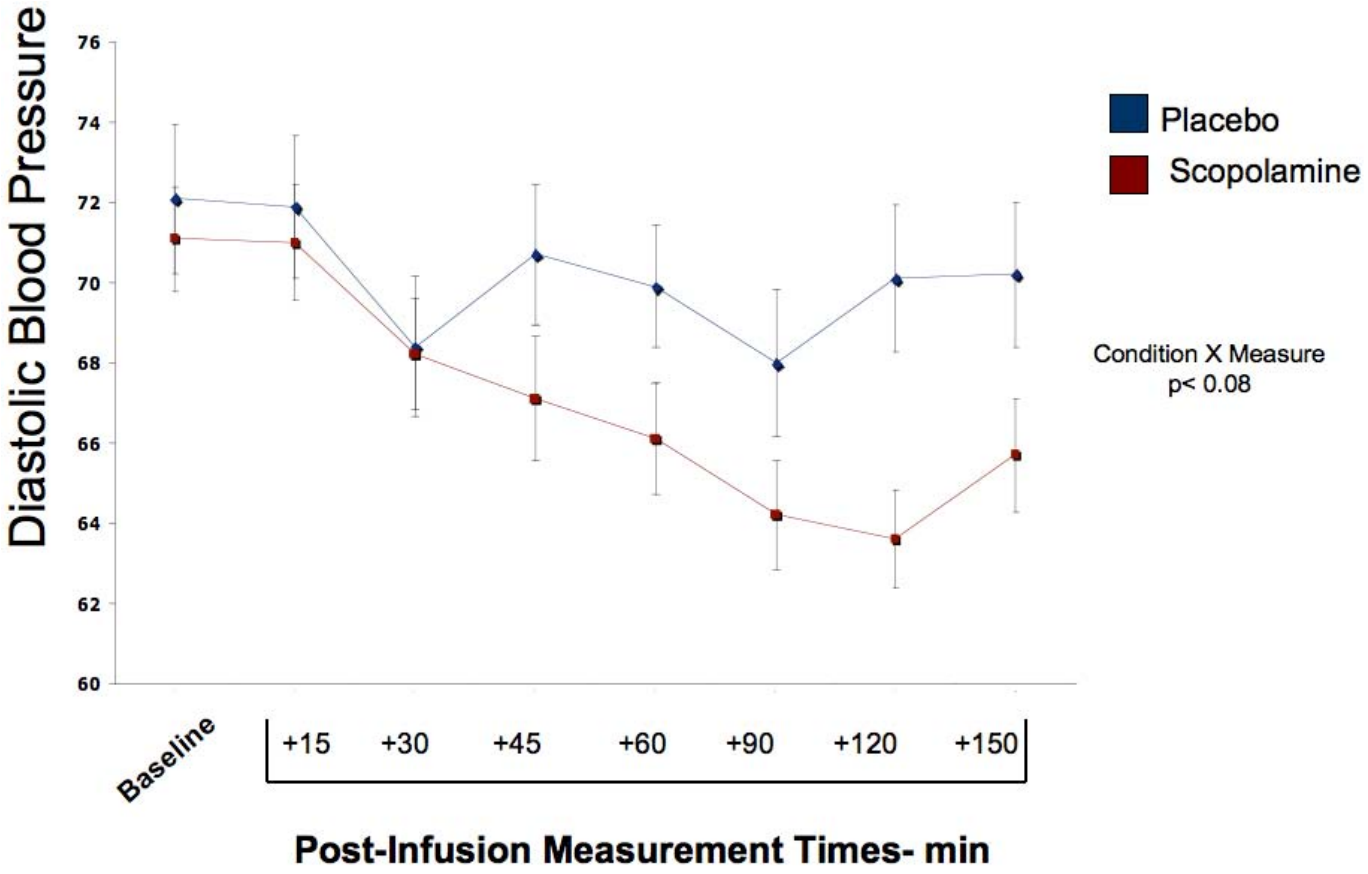

Figure S5. Mean diastolic blood pressure measures (± SE) across placebo (blue) and scopolamine (red) sessions are shown for time points between baseline and 150 min following the initiation of the infusion.