Lithium Continuation Therapy Following Ketamine in Patients with Treatment Resistant Unipolar Depression: A Randomized Controlled Trial

Supplemental Information

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Supplemental Methods

Screening

As part of the screening procedures, all participants underwent a medical clearance that included medical history and physical examination, EKG, clinical hematological and biochemical blood analyses, urine toxicology and urine pregnancy test for female participants.

Randomization and masking

A double-blind method in which the study participant, the rater, and study physician were blind to the treatment condition was utilized. Participants were randomized to lithium or placebo in blocks of four according to a 1:1 randomization schedule. Participants randomized to lithium received lithium carbonate ER 300 mg capsules while the participants randomized to the placebo condition were assigned to matching inert capsules. The randomization codes, study drug, and matching placebo were managed by the Investigational Drug Service (IDS) of the Mount Sinai Hospital. A co-investigator of the study not administering any outcome measures (L.S., the unblinded physician) was enlisted to check the participants' lithium serum levels and communicate with the pharmacy regarding dosing adjustments. Participants randomized to lithium started at 300 mg PO at night on Day 0 with instructions to increase the dose to 600 mg PO at night after two days in the absence of moderate to severe side effects. Five days following initiation of lithium, at Day 7, a morning blood draw was performed to obtain the circulating lithium level. An EKG was also conducted at this visit in order to monitor for any potential effects of lithium on cardiac function. The unblinded study physician received the lithium serum level results and contacted each participant to advise him or her to stay at 600 mg (if lithium blood level was in the target range) or increase the dosage to 900 mg. This co-investigator would communicate "stay" to the blind study team to alert the team when the participant remained on the lithium or his/her placebo dose of two pills following Visit 1, or "increase" to indicate that the participant was required to increase his or her daily lithium or placebo dose to three pills. To ensure that the communication of "stay" or "increase" for a given subject did not identify them as having been randomized to lithium, the unblinded co-investigator also communicated "stay" or "increase" for participants randomized to placebo based on a computer-generated random number sequence. Similar procedures were completed at the final ketamine infusion Day 11.

Statistical Analyses

Efforts were made to keep the percentage of missing data as small as possible, by attempting to conduct an exit interview with each participant who left the study prematurely in order to determine their MADRS score at study exit, their reason for study exit, and any adverse events that may have been related to

participation in the protocol. Missing values for the MADRS scores at the primary outcome were imputed from participants' baseline score.

Descriptive statistics were used for the secondary endpoints. Means, standard deviations, and 95% confidence intervals for the secondary outcomes by treatment group are reported. Differences were calculated between final and initial time points. Missing values were imputed from their baseline, as described above.

Supplemental Tables

Table S1. Concomitant Psychotropic and other Medications at Randomization in Study Sample

ID	Psychotropics at Randomization	Other Medications	Treatment Group
DD001	-	-	Lithium
DD004	Alprazolam	Fentanyl patch Hydromorphone Ondansetron	Lithium
DD005	Alprazolam Amphetamine/dextromoamphetamine Clonazepam Eszopiclone	None	Placebo
DD006	-	-	Placebo
DD008	Diazepam	Finasteride	Placebo
DD010	-	Dimenhydrinate	Lithium
DD011	Bupropion Clonazepam Quetiapine	Esomeprazole Omeprazole	Lithium
DD012	Aripiprazole Diazepam Doxepin Gapapentin Hydrocodone/Acetaminophen	Chlorthalidone Metaxalone Tizanidine	Placebo
DD014	Clonazepam	-	Placebo
DD016	Clonazepam Lorazepam Quetiapine	Liothyronine Minocycline Sumatriptan Tamsulosin	Placebo
DD017	-	Aspirin Tramadol	Lithium
DD020	-	Diphenoxylate-atropine Infliximab	Lithium
DD021	-	-	Placebo
DD022	Lorazepam Zolpidem	Metformin Naprosyn Simvastatin	Placebo
DD023	-	Levothyroxine	Lithium
DD025	-	Diphenhydramine	Lithium
DD026	Clonazepam Methylphenidate	Atorvastatin Clomiphene	Lithium
DD027	Clonazepam Temazepam Topiramate	Promethazine Diphenhydramine Ibuprofen Meloxicam Propranolol Sumatriptan	Lithium
DD028	-	Pregnenolone	Placebo
DD030	-	Albuterol	Placebo
DD031	Dextroamphetamine Diazepam Lisdexamfetamine Zolpidem	Beclomethasone Cyclosporine Drospirenone/ethinyl estradiol Fexofenadine Montelukast	
DD032	Clonazepam Zolpidem	-	Lithium
DD033	None	-	Placebo
DD034	Aripiprazole Clonazepam Lamotrigine Zolpidem	-	
DD035	-	-	Placebo
DD036	-	-	Lithium
DD038	-	Labetalol	Lithium
DD039	Alprazolam	Ibuprofen Labetalol Metformin	Lithium

DD040	Alprazolam Quetiapine	-	Lithium
DD041	-	Secukinumab	Placebo
DD042	-	Montelukast	Placebo
DD045	-	-	Placebo
DD046	Amphetamine/dextromoamphetamine Carbamazepine Diazepam Lamotrigine	Levothyroxine	Lithium
DD047	Clonazepam Gabapentin	Acetaminophen Aspirin Butalbital Fluticasone Oxycodone Propranolol Tizanidine	Lithium

Supplemental Figures

Figure S1. Consort Diagram