Targeted Treatment of Individuals with Psychosis Carrying a Copy Number Variant Containing a Genomic Triplication of the Glycine Decarboxylase Gene

Supplemental Information

Contents

Personalized Medicine Based on Genetically Informed Targeted Treatments in Psychiatry, Including Challenges and Broader Implications

Genetic discoveries and clinical genomics (1) have revolutionized the molecular diagnosis and treatment of many medical disorders, giving credence to the idea that precision medicine can both optimize treatment responses and minimize adverse effects. (2-4) And, for psychiatry, in particular, as Scolnick has written, “A key milestone …for the entire field - is to link a particular genetic variant …to the disease biology.” (5) Yet the abundance of recent, replicable findings in psychiatric genetic association studies contrasts with the striking absence of discoveries that have translated into improved clinical care, (6) the one exception being identification of the susceptibility allele for Stevens-Johnson syndrome. Screening prospective recipients of carbamazepine has virtually eliminated this potentially fatal side effect in parts of Southeast Asia. (4, 7)

As the present study illustrates, use of structural genetic variants is a promising approach. However, as also illustrated by the present study, convincing demonstration of treatment relevance of these variants in human studies is difficult to achieve, because even the most recurrent structural variants are individually rare, private mutations even more so. As a result, most studies will be variations of "n-of-1" treatment trials. (8, 9) Sample sizes will invariably be small and will usually be limited to one or a few families, a practical constraint on the feasibility of replications based on conventional sample size considerations. Nevertheless, rare variants, which have comparatively large effects, are more likely to be tractable if their mechanisms of action can be identified. If individuals with mutations in genes impacting glutamatergic and NMDAR signaling represent a molecular subtype, therapeutic benefit from compounds that enhance NMDAR function may not be limited to the *GLDC* mutation specifically, resulting in potentially larger sample sizes.

Even if the challenge of demonstrating efficacy for a given treatment based on a given structural genetic variant is overcome, the translation of this knowledge into clinical applications poses additional challenges. The development of medications to treat psychiatric disorders (so-called “tertiary prevention”) based on improved knowledge of pathophysiology is an obvious and not particularly controversial step. However, considering treatment of those with prodromal symptoms of disorder (“secondary prevention”) and even asymptomatic individuals at risk (“primary prevention”) raises important public health and ethical issues, a discussion of which is beyond the scope of this paper.

9p24.1 CNV Details

The complex rearrangement is located on a marker chromosome (10) and is made up of CNVs ranging in size from 400 bp to 1.15 Mb, with the most likely phenotype-related gene disruptions occurring in the first four CNVs (Figure 1A). The rearrangement was likely formed in the germline of the maternal grandmother. (11) The marker was not present in the proband's two siblings or in the mother's three siblings. Custom high-resolution array comparative genomic hybridization showed that the first set of CNVs spans (hg 19) chr9:5,273,771-7,129,163 and includes a 24 kb triplicated region (*RLN2*), a 1.15 Mb duplicated region (*RLN1*, *PLGRKT*, *CD274, PDCD1LG2, RIC1, ERMP1, MLANA, KIAA2026, RANBP6, IL33, TP52L3*, and *UHRF2* (partial)) and a 672 kb triplication comprised of *UHRF2* (partial), *GLDC*, and *KDM4C* (partial). Within this region, the glycine decarboxylase gene (*GLDC*), which encodes the GLDC enzyme, is fully triplicated. Genotypes of SNP rs10975641 of the *GLDC* gene, which is associated with selective serotonin reuptake inhibitor response, (12) were consistent with the *GLDC* triplication in the carriers (Figure S9). A smaller 64 kb intronic duplication [chr 9:9, 862,702-9,921,214 (minimum)/9,927,237 (maximum)] less than 2 kb from the nearest exon, contained part of the *PTPRD* gene (Figure S10).

Genes in the 9p24.1 Complex Genomic Rearrangement Region that Act in the Brain

RANBP6: The GTPase Ran regulates nucleocytoplasmic transport. Ran binding proteins (RanBP) regulate the guanine-nucleotide state of Ran, which regulates importin-dependent cytoplasmatic transport). (13) Importins are involved in regulating pathways connecting synaptic NMDA receptor signals to nuclear responses. (14) *RANBP6* is particularly noteworthy for being among the 8.5% of genes most intolerant of functional variation genome-wide (intolerance score: -1) (15) (http://genic-intolerance.org/); Residual Variation Intolerance Score (RVIS) based on ExAC sequencing data (16) 11.3% of genes most intolerant of functional variation. Intolerance score based on z-score distribution (16): 88 percentile (lower percentile corresponds with more *intolerant*).

KDM4C: Increased gene transcription resulting from overexpression of the *KDM4C* gene which encodes a histone trimethyl demethylase. The *KDM4C* gene is a histone trimethyl demethylase; ectopic expression leads to decreased histone methylation at the H3K9me3/me2 residues and a reduction of heterochromatin. (17) Overexpression of *KDM4C* may result in increased transcription and epigenetic changes in gene expression. Increased expression of Setdb1, a histone methyltransferase involved in transcriptional repression, was recently shown to be involved in the regulation of mood-related behaviors at loci that include the NMDAR subunit *NR2B/Grin2B*. (18) Notably, histone methylation has been implicated in schizophrenia (19) and a recent genome-wide association analysis found that histone methylation processes showed the strongest association with schizophrenia, major depression and bipolar disorder. (20) If overexpression of the *KDM4C* contributes to features of a neurodevelopmental phenotype, it could potentially be treated with *KDM4C* inhibitors. Intolerance score: -0.34; percentile: 29.6 (RVIS: 6.94 percentile based on ExAC sequencing data). Intolerance score based on Lek et al. (16) z-score distribution: 96 percentile.

UHRF2: UHRF2, an E3 ubiquitin ligase and a small ubiquitin-like modifier (SUMO) E3 ligase is a transcriptional target of the transcription factor E2F1 and is an important mediator of the apoptotic action of E2F1. (21) Thus, increased expression of *UHRF2* may promote apoptosis. Increased expression of apoptotic genes has been found in bipolar disorder but not in schizophrenia. (22) In addition, the association of GSK3β with E2F1 facilitates nerve growth factor-induced neuronal cell differentiation. (23) The GSK3β signaling pathway is a potential target of lithium (24, 25) and has been implicated in the development of neuropsychiatric disorders. (26, 27) Deletion is associated with decreased spatial memory mediated in the hippocampus. (28) Intolerance score: -0.38; percentile: 27.9 (RVIS: 7.39 percentile based on ExAC sequencing data). Intolerance score based on Lek et al. (16) z-score distribution: 5.5 percentile.

IL33: *IL33* is a member of the IL1-cytokine family and can form a complex with the transcription factor NFκB reducing binding of NFκB to its cognate DNA which results in a reduction NFκB-stimulated gene expression. (29) Astrocyte-derived IL33 was recently shown to be necessary for normal synapse number and neural circuit function in the spinal cord and thalamus. Deletion of *IL33* was associated with excess excitatory synapses, implicating deficient pruning, and a hyperexcitable intrathalamic circuit. (30) Intolerance score: 0.42; percentile: 77 (RVIS: 40.9 percentile based on ExAC sequencing data). Intolerance score based on Lek et al. (16) z-score distribution: 96.6 percentile.

GLDC: See text. Intolerance score: -0.67; percentile: 15.41 (RVIS: 29.71 percentile based on ExAC sequencing data). Intolerance score based on Lek et al. (16) z-score distribution: 95 percentile.

Intolerance and Percentile Scores of Other Genes within the Duplicated-Triplicated Region

Gene	Intolerance Score	Intolerance Percentile	ExAC RVIS percentile*	ExAC percentile
RLN2	0.35	74.4	89.4	76.1
RLN1	-0.09	46.7	77.9	76.8
CD274	0.37	75.1	38.6	35.8
PDCD1LG2	0.37	75.3	72.24	88.2
MLANA	-0.23	36.9	66.4	56.9
KIAA1432	-1.7	2.6	1.5	88.6
ERMP1	-1.04	7.8	7.5	87.2
TPD52L3	0.48	79.3	69.9	93.7
C9orf46 (*PLGRKT*)	0.22	67.9	54	95.6

Intolerance scores not available for *KIAA2026*

* Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [August, 2016].

Glycine Augmentation Trials

Subject Information. At the beginning of the acute glycine augmentation trial, the two participants included one female, age 59 (5459) with a diagnosis of bipolar disorder with psychotic features, and one male, age 31 (3363) with a diagnosis of schizo-affective disorder. By the end of the chronic glycine arm of the study, 5459 was 61 years old and subject 3363 was 33 years old. DSM-IV (31) diagnoses were based on a Structured Clinical Interview for DSM-IV interview, (32) which was supplemented by hospital records and family informant information. A group of four senior clinicians reviewed all clinical material and assigned consensus diagnoses blind to genotype status.

Medication Information. During all three arms of the acute glycine trial, medications were kept stable: 3363 - clozaril (100 mg/d), aripiprazole (15 mg/d), celexa (40 mg/d); 5459 - clozaril (50 mg/d), lithium (450 mg/d), gabapentin (300 mg/d), cymbalta (120 mg/d). Within 9 weeks of the end of the acute glycine trial, subject 5459's dose of clozaril was increased from 50 mg/d to 62.5 mg/d due to worsened psychotic symptoms; the dose remained between 62.5-75 mg/d until week 15 of the chronic glycine study when it was lowered to 50 mg/d. The same subject took mirapex (0.03125-0.375 mg/d) for restless legs as of week 4, day 5 for the duration of the chronic glycine study. In all other respects, psychotropic drugs and doses were the same during the chronic trial as during the acute trial.

Additional Clinical Effects. Short-term Glycine Trial. Subject 3363 showed improvement in both positive psychotic and negative symptoms. Improvement in subject 5459, who had no negative symptoms, was restricted to positive and mood symptoms. For both subjects, CGI ratings changed from a baseline rating of moderately ill to borderline or mildly ill during glycine administration; placebo ratings were the same as at baseline (Figure S11).

Management of Side Effects. Both subjects developed GI side effects during one arm of the double-blind crossover and during treatment with open-label glycine; no GI side effects were experienced during the placebo arm. Both subjects also developed GI side effects during the chronic glycine trial. When these side effects occurred, the next dose or two were held and the subject was re-started on a well-tolerated lower dose, usually within a day (see Tables S1-6 for more details).

Tolerability of Glycine

Acute Clinical Trial

Since every dose of glycine and placebo had to be made by hand by the pharmacy due to the blind, target doses (0.8 gm/kg) for each treatment arm during the acute clinical trial were based on the subject's weight approximately five weeks prior to the beginning of a treatment arm. Due to minor weight fluctuations and glycine tolerability during these two acute exposures to glycine, the *de facto* target and sustainably tolerable doses varied (see table below). The maximum sustainably tolerable dose was about 76.2-85% of the optimal dose recommended in the literature. During the chronic glycine trial, the GI side effects became a rate-limiting factor and the maximum sustainably tolerable doses were substantially lower (18.8-27.5%) than the optimal dose recommended in the literature.

Chronic Glycine Trial

Dose Titration. Starting with a dose of 5.4 gm (1.8 gm TID), the dose was titrated upward toward the planned target doses of 26 gm TID (78 gm/d) for 5459 and 28.8 gm TID (86.5 gm/d) for 3363. Neither subject was able to reach the target dose without developing GI symptoms (Tables S7, S7a, S8, S8a) necessitating dose adjustments. Subject 3363 was able to reach 18 gm TID (0.5 gm/kg) - and subject 5459 was able to reach 18-21 gm TID (0.56-0.67

gm/kg) during the first 16 weeks of the chronic trial but with varying degrees of tolerability of TID dosing. As a result, each began to skip at least one dose/day on a semi-regular basis. After 16 weeks, they requested a respite from the glycine regimen.

Subjects 3363 and 5459 reached doses of 54 gm/d (0.5 gm/kg) and 54-63 gm/d (0.56-0.67 gm/kg), respectively, during the first 16 weeks. Due to the re-emergence of symptoms after glycine discontinuation at 16 weeks, 5459 requested to re-start glycine after 18 days off it and the titration schedule was re-initiated. The highest dose that could be sustained without side effects was 39 gm/d (0.387 gm/kg) for 7 weeks, after which GI side effects required even lower doses for the remainder of the study (Table S8). After 63 days off glycine, 3363 also requested to resume; the highest tolerable dose for any sustained period of time was ~25 gm/d (0.216 gm/kg) (Table S7). Although the target doses had been 26 gm TID (78 gm/d) for 5459 and 28.8 gm TID (86.5 gm/d) for 3363, neither subject was able to reach the target dose without developing GI symptoms, necessitating dose adjustments. Overall, the maximum tolerable doses were 18.8-27.5% of the target dose (see table below).

	3363	**5459**
Target dose – double-blind glycine	0.78 gm/kg	0.84 gm/kg
De facto tolerable dose – double-blind glycine	0.64-0.70 gm/kg	0.70-0.84 gm/kg
Target dose – open-label glycine	0.75 gm/kg	0.78 gm/kg
De facto tolerable dose – open-label glycine	0.61 gm/kg	0.68 gm/kg
Target dose – chronic glycine	0.60 gm/kg	0.66-0.68 gm/kg
De facto tolerable dose – chronic glycine	0.22-0.50 gm/kg	0.15-0.38 gm/kg

Acute Clinical Trial Notes

As shown in Table S5, family expressed concern about a possible exacerbation of psychotic symptoms in subject 3363 on day 5 of week 3 of glycine augmentation. To be cautious, we held one dose and reduced the next dose, and then slowly titrated the dose of glycine back up over the next several days. The subject denied an exacerbation of symptoms, but reported that he was suddenly experiencing very few intrusive thoughts, including fewer thoughts of any kind, which he found disconcerting. He experienced a notable reduction in positive symptoms shortly afterward.

Plasma Levels

Glycine Augmentation Trial

Three baseline plasma levels were obtained for small (excitatory) amino acids and two baseline plasma levels were obtained for large (branch-chain) plasma amino acids, kynurenine (KYN), kynurenic acid (KYNA), quinolinic acid, homocysteine, and GABA. Tryptophan, KYN, KYNA, and quinolinic acid plasma levels were assessed because the kynurenine pathway of tryptophan degradation impacts NMDAR function (33). Homocysteine (Hcy) plasma levels were obtained because Hcy is an agonist of the NMDAR, but acts as a partial antagonist when glycine concentrations at the GMS are low. (34) Total serine levels were obtained as part of a small (excitatory) amino acid assay; in addition, in a separate assay, D-serine and L-serine were measured separately and total serine was calculated as the sum of D-serine (1-4% of total serine) and L-serine (96-99% of total serine). The two methods of calculating total serine were highly correlated ($r = 0.965\text{-}0.9925$, $P<0.001$) and are essentially interchangeable. The table below summarizes the % increases in glycine, total serine (D+L-serine), D-serine, and L-serine levels. Glycine and L-serine plasma levels are shown in Figures 3A-3D.

During the acute clinical trial, plasma levels were repeated in week 6 of each treatment arm and in the final week of the 2-3 week period between treatment arms. During the chronic glycine clinical trial, plasma levels were obtained at baseline, at monthly intervals, and two weeks after the end of the trial. Psychotropic drug plasma levels were obtained at the same time points.

Percent change in total serine and glycine levels during treatment with glycine was calculated using the mean of the baseline values.

Percent Increases in Plasma Glycine, Total Serine, L-Serine- and D-Serine during Double-Blind (DB) and Open-Label (OL) Exposure to Glycine Augmentation

	% Increase in Plasma Level			
	Glycine	Serine	L-Serine	D-Serine
DB Glycine - 3363	166%	170%	171%	118%
DB Glycine -5459	122%	145%	146%	105%
OL Glycine -3363	121%	156%	159%	47%
OL Glycine -5459	179%	205%	210%	95%

Other than the changes noted in the text, no changes outside the normal range were observed in other small amino acid levels or in any of the large branch-chain amino acid plasma levels at baseline or in the various drug conditions. Plasma tryptophan, GABA and glutamine plasma levels were within the normal range, although at the low end of it, throughout the study. Glutamic acid and homocysteine plasma levels were also within the normal range. Quinolinic acid plasma levels were within the normal range in both subjects, but at the high end of that range in 5459 and did not vary as a function of exposure to glycine.

DCS Augmentation Trial

Total serine as measured in the small amino acid assay is reported. Notably, DCS plasma levels during the first open-label exposure were well below the ~5.5ug/mL (54uMol/L) reported by Goff et al. in a patient who dropped out of a DCS augmentation trial due to worsening clinical symptoms. (35)

Quinolinic acid plasma levels were within the normal range in 3363, but were elevated at baseline in 5459 and normalized on DCS but this reduction was not sustained during chronic exposure to DCS. Hcy plasma levels were within normal range throughout the study.

Both Augmentation Trials

Psychotropic drug plasma levels were within the therapeutic range at all time points. Lithium level remained stable at 0.4-0.5 mEq/L throughout the study.

Methods

Small Excitatory Amino Acids

Plasma glutamic acid, serine, glycine and glutamine were determined using a modified liquid chromatographic procedure (36) that used O-methylserine as the internal standard. Plasma (0.25mL) was deproteinized and extracted prior to derivatization with PITC reagent to enhance separation and detection at 254 nm. Calibration standards that include the expected concentration range preceded each batch of samples as well as a set of quality controls to validate each day's analyses. Based on previous data, inter-assay variability for glutamic acid, serine, glycine and glutamine did not exceed 8.4%, 2.8%, 4.0%, and 10.5%, respectively, for the low quality controls, and 5.4%, 2.8%, 8.0%, and 9.9%, respectively, for the high quality controls (n = 6 days). Intra-assay variability for the same amino acids did not exceed 7.3%, 1.4%, 1.2% and 2.1%, respectively, for the low quality controls, and 6.2%, 5.4%, 3.0% and 5.1%, respectively, for the high quality controls (n = 12).

Large Neutral Amino Acids

Plasma large neutral amino acids were measured using a gradient liquid chromatographic procedure (36) with norleucine as the internal standard. Plasma (0.25mL) was deproteinized and extracted prior to derivatization with PITC reagent to enhance separation and detection at 254 nm. Calibration standards that include the expected concentration range preceded each batch of samples as well as a set of quality controls to validate each day's analyses. Inter-assay variability for all the amino acids measured did not exceed 14% (n = 25 days).

Plasma *d*-serine

Plasma *d*-serine was determined using liquid chromatography with fluorescence detection. The procedure was based on the formation of a fluorescent diastereomeric derivative formed from the pre-column addition of o-phthalaldehyde and BOC-*L*-Cys. (37) To 100 μl of plasma or serum sample, the internal standard (*l*-homocysteic acid) was added, with acetonitrile, vortexed and centrifuged. Following evaporation of the supernatant, the residue was re-dissolved in borate buffer and allowed to react with the derivatizing reagent. Immediately following the reaction, the mixture was injected onto a C-18 column (Nova-Pak, Waters Corp.) and eluted using a complex gradient elution program consisting of an acetate buffer and acetonitrile. The separated components were detected using an Agilent Model 1321A Fluorescence Detector set at $\lambda_{excit.}$ = 245nm and $\lambda_{emiss.}$ = 470nm. The resulting retention times for the internal standard and d-serine were 18.8 min., and 24.8 min., respectively. The total run time between samples was about 70 minutes, including equilibration time and on-line derivatization. Intra-assay variability did not exceed 6.4% for the 7 calibration concentrations of d-serine (n = 8 for each concentration). Inter-assay variation did not exceed 9.1% based on 2 sets of quality controls included with each run (n = 13 days)

Plasma Tryptophan

Total plasma tryptophan was measured using a validated unpublished liquid chromatographic procedure that used native fluorescence of tryptophan for detection. An internal standard 5-methyltryptophan was added to the plasma sample (0.25 mL) followed by deproteinization and centrifugation. An aliquot of the supernatant was injected on the column. Using a phosphate buffer (pH = 4.7) and acetonitrile as the mobile phase with a reversed phase ODS column (15 x .39 cm, 4 μm Novapak, Waters Corp.), tryptophan and the internal standard were eluted in less than 12 minutes. Fluorescence detection was optimized using an excitation wavelength at 290 nm and analyzed at 340 nm. Inter-assay variability of plasma tryptophan did not exceed 5.1% for the low quality controls, and 7.2% for the high quality controls (n = 22 days).

Plasma GABA

An HP Chemstation data system was used to control an HP 5988B GC-MS system and to collect and quantify the data. The GC-MS with a DB-1 column (15 m x 0.25 mm I.D., 0.25 μm) was operated in the NCI mode using methane: ammonia (95:5) as the reagent gas. The column was programmed from 80°C (holding for 1 min) to 160°C at an increasing rate of 22°C/min and then to 260°C at a rate of 30°C/min. The ion-source temperature was 150°C, and the temperatures of the injector (splitless) and the interface between the chromatograph and the spectrometer were set to 265°C. The extraction method was modified from a previous publication. (38) An internal standard GABA-d_6 (15 ng) was added to 0.5 ml of plasma sample followed by addition of 0.8 ml of 1 M phosphate buffer (pH 11.5) and 50 μl of methyl chloroformate. After shaking for 10 min, 150 μl of 6 N HCl and 4 ml of ethyl acetate were added. The mixture was mixed for 10 min and centrifuged. The supernatant was transferred to a round

bottom tube and dried down. To the residue, 10 μl of triethylamine and 100 μl of 15% pentafluorobenzylbromide in acetonitrile were added. The mixture was allowed to stand at room temperature for 30 min and was extracted with 200 μl of 0.5 N HCl and 1 ml of hexane. The supernatant was transferred and dried down. The residue was dissolved in 30 μl ethyl acetate and 2μl injected for GC-MS analysis. The molecular ion peaks, $[M]^+$ at m/z 160 from GABA and at m/z 166 from deuterated GABA were used for quantitation, and the fragment peaks at m/z 128 and at m/z 134 were used as confirming ions, respectively. The calibration standard with range of 0.5 to 60 ng/ml of GABA and quality controls were run with each day's analysis. The inter-assay precision of the method was determined by testing the blank plasma containing 6.25, 12.5 and 25.0 ng/ml GABA on six separate days. The relative standard deviations (RSD) were 6.3%, 5.2% and 5.7%, respectively.

Plasma Citalopram and Metabolites

Plasma citalopram and two metabolites, desmethyl- and didesmethylcitalopram, were measured using a previously published liquid chromatographic method. (39) The procedure was modified slightly by using a more polar reversed-phase column (trimethylsilyl bonded silica) and altering the mobile phase to 72:28 phosphate buffer:acetonitrile with the pH adjusted to 3.2 with phosphoric acid and n-butylamine with a flow rate at 1.5 ml/min. A fluorescence detector set at $235nm_{excit.}$ and $300nm_{emiss.}$ resulted in clean chromatograms with no interference from other drugs or endogenous material. The method was validated from 300 ng/ml to the lower limit of quantitation (2.5 ng/ml), resulting in an intra-day variation of no more than 10% for all three compounds at seven concentrations of the calibration curve. Inter-day variation did not exceed 6.8% for the three quality controls over 16 consecutive days.

Plasma Kynurenic Acid

Plasma concentrations of kynurenic acid (KYNA) were determined using a modified validated method. (40) Plasma (0.25 mL) was treated with 3.4M perchloric acid, vortexed and centrifuged at 13,000 rpm. Fifteen microliters of the supernatant was injected for chromatographic analysis. The chromatographic system employed a Supelcosil octasilyl LC-8 column (75 x 3.0 mm, 3µm particle size) with a mobile phase consisting of 92% (v/v) ammonium acetate and zinc acetate (50 mmol/L each; pH adjusted to 6.5), and 8% (v/v) methanol. A flow rate of 0.55 ml/min. elutes KYNA at ~ 3.9 min., and was detected using an Agilent Model 1321 Fluorescence Detector operating at λ_{ex} = 251nm and λ_{em} = 398nm. A 7-point calibration curve encompassing the expected concentration range of KYNA was included with each run.

Plasma Quinolinic Acid

Plasma quinolinic acid (QUIN) was measured using a gas chromatography-mass spectroscopy (GC/MS) procedure employing a deuterated internal standard (quinolinic acid-d7) for quantitation. Following the addition of the internal standard to 0.5 mL of plasma, perchloric acid was added for protein precipitation and then centrifuged. Ethyl acetate was added to the supernatant to extract QUIN, then derivatized with trifluoroacetylimidazole for 1 hour at 80°C. An aliquot of the derivatized extract was injected onto a DB-5, 30 cm column using negative chemical ionization for detection of molecular ions. A six-point calibration that encompassed the expected plasma concentrations (4 - 200 ng/mL) was included with each sample set.

Plasma Kynurenine

Plasma kynurenine (KYN) was assayed using a modified liquid chromatography method with UV detection. (41) Following protein precipitation with 3.4 M perchloric acid, 50 µL of the clear supernatant was injected on a reverse-phase column Phenomenex Luna C-18, 3µm and eluted with a phosphate buffer and acetonitrile at a flow rate of 1.2 mL/min. KYN was detected

at 226 nm with a retention time of 6.8 minutes. A six-point calibration curve that encompassed the expected concentrations (0.5 – 10 μM) was included with each run.

Plasma Total Homocysteine (tHcy)

Plasma homocysteine (tHcy) was determined using a modified published liquid chromatographic procedure validated in our laboratory. (42) Using penicillamine as the internal standard, 0.4 ml of plasma sample was reduced with dithiothreitol at 37°C for 15 minutes. Following the addition of sulfosalicylic acid, the sample was centrifuged and the supernatant transferred to the liquid chromatograph for separation and quantitation. tHcy and the internal standard were separated isocratically using a reversed-phase octyldecylsilyl 5μm particle column and a mobile phase consisting of diammonium hydrogen phosphate, and methanol with octanesulfonic acid as an ion-pairing reagent. At a flow rate of 1.4ml/minute, the two compounds were detected using dual-electrode coulometric detection at a potential of +1.1V (vs. a proprietary reference electrode) at a run-time of 25 minutes. A six-point calibration curve encompassing the anticipated range of plasma homocysteine was generated. Chromatographic data were collected using a PC-based chromatography software program. Intra-day variation did not exceed 8% for all six calibration levels (n = 8 each), with a low limit of quantitation of 5 nM/mL.

Plasma Clozapine and Norclozapine

Plasma clozapine and norclozapine were determined by a validated liquid chromatographic procedure with UV detection. Following the addition of two internal standards, mianserin and metiapine, to a one ml plasma sample, one ml of sodium hydroxide (0.5M) and 4 ml of 10% isoamyl alcohol in hexane were added and mixed for 10 minutes. After centrifugation at 2000 rpm for 10 minutes, the supernatant was transferred to a tube containing 150μl of 0.1M

phosphate buffer (pH~ 2.2), mixed for 10 minutes and centrifuged for 10 minutes. The organic phase was aspirated to waste and the aqueous extract was transferred to injection vials. Chromatography was carried out using a Supelcosil HS-F5 bonded silica-based column (250 x 4.6mm, 5μm particles) with a mobile phase consisting of 68% phosphate buffer and 32% acetonitrile modified with n-butylamine and phosphoric acid to adjust the pH to ~ 2.5. The flow rate at 1.5 to 1.7 ml/min eluted all 4 compounds within 12 minutes using a UV detector set at 245 nm. The calibration curves were linear from 25 to 2000 ng/ml for clozapine and norclozapine. Intra-day variation for norclozapine and clozapine did not exceed 7% and 4%, respectively, for the seven calibration concentrations (n = 10 at each concentration). Inter-day variation for norclozapine and clozapine did not exceed 10% (n = 11 days), based on three sets of quality controls (1500, 750, and 75 ng/mL) in duplicate added to each day's run to determine acceptability of the data.

Plasma Aripiprazole & Dehydroaripiprazole

Plasma aripiprazole and its major active metabolite were assayed at the Analytical Psychopharmacology Laboratory, Nathan Kline Institute, using a recently validated procedure employing liquid chromatography with UV detection. A 1 ml plasma sample, with internal standard protriptyline added, was alkalinized with sodium hydroxide and extracted with 1.5% isoamyl alcohol in heptane. Following back-extraction into acidic phosphate buffer, an aliquot of this extract was injected onto a reversed phased C-8 column and eluted with a mobile phase of phosphate buffer and acetonitrile. At a flow rate of 1.5 ml/ml, aripiprazole, internal standard, and dehydroaripiprazole were detected at 215 nm, at 5.8, 6.9 and 8.1 minutes, respectively. A nine-point calibration curve with a range of 5 to 800 ng/ml was included with each batch of samples. Intra-assay variation did not exceed 12% (n = 8 for each concentration). Inter-assay variation, assessed using three levels of quality controls for each compound, did not exceed 12.5% (n = 6 days).

Plasma Duloxetine

Plasma duloxetine was analyzed using a procedure developed for fluoxetine. (43) To one mL of plasma, the internal standard, maprotiline, was added, made alkaline with sodium hydroxide, and extracted with isoamyl alcohol in heptane. Following a 10 minute mix and centrifuging, the extract was evaporated to dryness, and the residue derivitized with dansyl chloride. The reconstituted residue was chromatographed on an octadecysilyl column with a mobile phase of water, acetonitrile and methanol, and with n-butylamine and phosphoric acid added. The compounds of interest were detected using a spectrofluorimeter with λ_{excit} = 255nm and λ_{emiss} = 515nm. The calibration standards ranged from 500 to 10ng/mL. The intra-assay variation for all seven calibration standards did not exceed 5% (n = 8 for each standard). Inter-day variation did not exceed 5% (n = 5 days).

Plasma Gabapentin

An HP Chemstation data system was used to control an HP 5988B GC-MS system and to collect and quantitate the data. The GC-MS with a DB-5 column (15 m x 0.2 mm I.D., 0.25 μm) was operated in a NCI mode using methane: ammonia (95:5) as the reagent gas. The column was programmed from 80°C (holding for 1 min) to 280°C at an increasing rate of 30°C/min. The ion-source temperature was 150°C, and the temperatures of injector and the interface between the chromatograph and the spectrometer were set at 280°C. The internal standard deuterated gabapentin (250 ng) was added to 0.1 ml of plasma sample, followed by addition of 0.2 ml of 0.5 M perchloric acid and then centrifuged. The supernatant was transferred to a round bottom tube, and 70 μl of 10 M KOH and Dowex AG 50 W 8x (~30 mg) were added. The content of the tube was mixed on a rotation shaker for 10 min. After centrifuging, the supernatant was discarded, and 0.2 ml of 1 N HN_4OH was added to the Dowex

precipitate twice, and gabapentin was eluted from the Dowex. The combined eluents were evaporated to dryness in a vacuum centrifuge. The residue was derivatized with 50 μl HFBA and 10 μl TFE at 65°C for 30 min, and was dried down. The residue was dissolved in 40 μl of ethyl acetate and 2μl was injected for GC-MS analysis. The molecular ion peaks, $[M]^+$ at m/z 409 from gabapentin and at m/z 412 from deuterated gabapentin, were used for quantitation, and the fragment peaks at m/z 329 and at m/z 332 were used as confirming ions, respectively. The standard curve was fitted to a quadratic equation with the curve encompassing a range of 10 – 1500 ng/100 μl for gabapentin with a negligible intercept. The curve and quality controls were processed similarly with each batch of samples. The inter-assay precision was determined by testing the plasma controls containing 120, 600 and 1200 ng/100 μl of gabapentin on five separate days. The RSD were 4.8%, 3.0% and 5.9%, respectively.

Dose Preparation of Glycine and Placebo/ Average Dose per Arm

Dose Preparation and Administration of Glycine in the Acute Clinical Trial

Each dose of glycine or placebo was prepared by hand in the McLean Hospital Research Pharmacy using the titration schedules in Tables S1a-6a. The placebo was a mixture of Isomaltulose (palatinose® PST-N:Palatinose® PST-PF; 3:1 proportions) provided by Beneo, Inc..

Subject 5459 received glycine (target dose: 76 gm/d) during arm 1 and placebo during arm 2; subject 3363 received placebo during arm 1 and glycine (target dose: 79.6 gm/d) during arm 2. The titration schedules (actual and planned) for each subject for each arm of the acute augmentation trial are included in Tables S1-6 and S1a-6a, respectively. During the open-label glycine trial, the target dose for subject 5459 was 71.6 gm/d; for subject 3363, the target dose was 81.8 gm/d. The maximum sustainably tolerable doses were ~76-85% of the target doses during both short-term exposures to glycine.

Each dose consisted of a bottle containing the glycine or placebo dose (bottle A) and a separate bottle containing the flavoring additives for each dose (bottle B). True Citrus lemon crystals were used as a flavor additive to counteract the sweetness of the glycine and placebo. Because the placebo was sweeter than glycine, the flavoring formulations for the glycine doses also included a small amount of sucralose to make the two substances taste indistinguishable when mixed with lemon crystals and water. At the time of administration, each glycine/placebo dose was prepared by pouring the contents of the flavoring bottle (B) into the glycine/placebo bottle (A) and adding cold distilled water to a specific fill line on the back of bottle A (Figures S12A and S12B). The final volume for each dose was calculated and marked on the bottle as the ‘fill line,’ such that each reconstituted dose would result in a 20%(w/v) glycine or placebo

solution (0.2 gm glycine or placebo per mL of solution). For example, a dose of 20 gm of glycine or placebo would have a final reconstituted dose volume of 100 mL.

At the time of each dose, the subject poured the flavoring into the bottle containing that dose of glycine or placebo and added water to the specified fill line. The bottle was then shaken vigorously for several minutes and the dose was slowly sipped until all of it was consumed. All doses were taken after a meal to minimize nausea and GI distress. The two bottles containing each dose were packed in a small sealed baggie and the three baggies corresponding to that day's doses were packed in a large baggie, labeled week 1, day 1, etc. A two-week supply of doses was shipped to each subject with week 2's doses on the bottom layer and week 1's doses on the top layer of the shipping box (Figure S12C). Each week of the study started on a Sunday and ended on a Saturday. Each subject also kept a daily log sheet that specified week 1, day 1, day 2, etc for each arm. These features made it straightforward for subjects to know which day corresponded to that day's dose. The packaging allowed subjects to conveniently carry a given dose or the entire day's doses if planning to be away from home during part or all of the day.

When it was necessary to lower the amount of a prepared dose due to the emergence of side effects, the subjects were instructed to mix the dose as usual, shake it up and then to pour a specified number of cc's of liquid into a calibrated cylinder that had been provided and to dispose of the poured out liquid. The lower dose was then re-shaken and consumed. Dose reductions required calculating the new final dose volume of the 20% (w/v) glycine/placebo solution (0.2 gm glycine or placebo/mL of solution) and instructing subjects to discard excess amounts.

Dose volumes were calculated as follows:

$$\text{Dose volume (mL)} = \frac{\text{\# gm glycine or placebo}}{\text{0.2 gm glycine or placebo/mL of solution}}$$

The appropriate amount of each dose reduction was determined by the study psychiatrist (JAB) and PI (DLL) based on the subject's recent history of side effect-free dosing; the specific number of cc's to be poured out and discarded so as to result in a correct new dose was calculated by the McLean Hospital Research Pharmacist (LJG). These dose reductions were carried out during a phone call between the subject and the PI to make sure that the method was correctly understood.

Throughout the study, the PI was in possession of a sealed envelope prepared by the McLean Hospital Research Pharmacist in case it became necessary to break the blind due to untoward side effects. The blind remained unbroken throughout the study and the sealed envelope was returned to the pharmacist at the end of the study (Figure S12D).

All empty containers were returned to the pharmacy at the end of the study for disposal (Figure S12E).

Dose Preparation and Administration of Glycine in the Chronic Clinical Trial

Glycine was supplied by Letco Pharmaceuticals. The McLean Hospital Research Pharmacy dispensed 500 gm and 1 kg jars of glycine to each subject with calibrated measuring utensils (teaspoons/tablespoons, mixing containers, graduated cylinders), TrueCitrus Lemon and Lime flavoring packets, and instructions for measuring and mixing each dose according to a prepared titration schedule (Figure S12F; Tables S7a and S8a).

At the time of administration, subjects prepared doses by combining specified amounts of glycine powder and distilled water, to result in the correct volume of 20% glycine solution (w/v) (0.2 gm glycine/mL of solution) for each dose and flavored it to taste.

The same procedures described above were repeated when doses had to be reduced due to GI side effects.

Average Dose per Arm

The mean daily dose (gm) and mean gm/kg dose for each arm and each subject are shown in the table below. During the acute trial, neither the mean daily dose nor the mean gm/kg differed in the double-blind and open-label arms for either participant (P > 0.20 for each). Both the mean daily dose and the mean gm/kg in the acute glycine treatment arms were significantly higher than in the chronic glycine arm for each participant (P < 0.001 for each).

Mean Daily Dose (gm) and Mean gm/kg Dose for Each Glycine Treatment Arm

	3363 Mean Daily Dose (gm) ± s.d.// mean gm/kg ± s.d.	5459 Mean Daily Dose (gm) ± s.d.// mean gm/kg ± s.d.
Acute Double-blind Glycine Arm	54.18 ± 22.11 // 0.53 ± 0.22	53.07 ± 22.09 // 0.58 ± 0.24
Acute Open-label Glycine Arm	55.28 ± 19.63 // 0.51 ± 0.18	53.33 ± 18.86 // 0.58 ± 0.21
Both Acute Glycine Arms	54.73 ± 20.79 // 0.52 ± 0.20***	53.20 ± 20.37 // 0.58 ± 0.22***
Chronic Open-Label Glycine	34.27 ± 13.65 // 0.31 (± 0.13)****	30.01 ± 16.59 // 0.31 (± 0.17)****
*** range:	(6.00, 81.90) // (0.06, 0.78)	(6.00, 75.90) // (0.07, 0.84)
**** range:	(3.60, 64.80) // (0.03, 0.60)	(5.00, 63.00) // (0.05, 0.67)

DCS Augmentation Trials

Compared with glycine, DCS has 65% activity at NMDAR containing the NR2B subunit, 90% activity at NMDAR containing the NR2A or NR2D subunit and 200% activity at NMDAR containing the NR2C subunit. (44) Each trial included a double-blind placebo-controlled phase and open-label phases.

Subject Information

At the beginning of the DCS augmentation trial, the two participants included one female, age 62 (5459) with a diagnosis of bipolar disorder with psychotic features, and one male, age 34 (3363) with a diagnosis of schizo-affective disorder. By the end of the chronic DCS arm of the study, 5459 was 63 years old and subject 3363 was 35 years old.

Medication Information

During all arms of the DCS trial medications were kept stable: 3363 - clozaril (100 mg/d), aripiprazole (15 mg/d), celexa (40 mg/d); 5459 - clozaril (50 mg/d), lithium (450 mg/d), gabapentin (300 mg/d), cymbalta (120 mg/d), mirapex (0.375 mg/d)*; phendimetrazine (35 mg/d)*.

Additional Clinical Effects

Data from other symptom domains (PANSS) salient for 5459 and 3363 are shown in Figures S13A-C and Figures S13D-G, respectively, and in Figure S14. On the CGI, both subjects went from moderately ill to borderline ill and symptoms were very much improved during exposure to DCS; placebo ratings were the same as baseline (Figure S15).

* Change in psychotropic drug/dose compared with one or all glycine trials.

Neurocognition

The MATRICS Consensus Cognitive Battery (45) was administered at baseline, in week 6 of each of the three arms of the acute glycine study, at the end of weeks 16 and 27 of the chronic glycine study, and in week 8 of the first open-label exposure to DCS. Since no consistent changes in neurocognition were observed as a function of glycine or DCS exposure, MATRICS testing was discontinued. See Figure S7 for scores on the MATRICS cognitive domains and overall composite score.

Associations between 9p24.1 Region and Neuropsychiatric Disorders

Schizophrenia

SNPs within 20 kb of the *GLDC* and *KDM4C* genes had potential associations ($P < 1 \times 10^{-4}$) with schizophrenia. (46) Two patients in a schizophrenia cohort at Duke had deletions overlapping the same 9p24.1 region. (47) Sequencing of one of these patients (from Rujescu) by the Lupski lab shows that *GLDC*, *IL33*, *TD52L3*, and *UHRF2* are completely deleted and *KDM4C* is partially deleted (Figure S16). In another report, a schizophrenia proband had a duplication of most of GLDC and part of *KDM4C*. (48) Xu et al. described a paternally inherited 1042.2 kb duplicated region on 9p24.1 (4,968,475-6,005,618) in a schizo-affective proband; this CNV included ten genes that overlap with the rearragement reported here, but did not include *IL33*, *TP52L3*, *UHRF2*, *GLDC*, and *KDM4C*. (49) Stewart et al. reported a full duplication of *GLDC* and a partial duplication of *UHRF2* and *KDM4C* in a patient with diagnoses of schizophrenia and idiopathic epilepsy. (50) The recent rare CNV analysis of a cohort of 20k schizophrenia cases and 20k controls from the Psychiatric Genetics Consortium reported *GLDC* duplications in 12 cases and 5 controls ($P = 0.1$). Most were partial duplications of the first several exons. There was only one case with a duplication of the entire *GLDC* gene, (51) underscoring the relative rarity of this CNV.

Bipolar Disorder

In addition to the original report of our duplication-triplication, (52) Priebe et al. described duplications of *GLDC* and *KDM4C* in bipolar disorder with age of onset ≤ 21. (53) Madison et al. described a >100 kb CNV deletion at 9p24.1 near Malhotra et al. 2011 but not identical - in one bipolar proband and one unaffected parent, but it is not clear what genes were included. (54)

Depression and Suicide Attempts

Large Arab Bedouin kindred with high rate of in-breeding. Duplication of *UHRF2* and *GLDC* is associated with increased risk for suicide attempts: OR of 5.4-13.1 Duplication is incompletely penetrant. Duplication or deletion of full *GLDC* gene. (55)

Autism Spectrum Disorder (ASD)

An ASD cohort had rare CNVs impacting genes in the 9p24.1 region: deletions (4) or duplications (1) in *RLN1* and *RLN2*, two deletions in *GLDC* (maternally inherited), and one duplication (maternally inherited) and one deletion (*de novo*) of *KDM4C*. (56) A later study of an ASD cohort by the same group reported a partial *GLDC* duplication in one simplex proband (maternally inherited), and a partial *GLDC*+ *KDM4C* duplication in one simplex proband (paternally inherited) and in one multiplex (maternally inherited) proband. (57) A study of SNPs in the 9p24 and 11p12-p13 regions containing glutamate metabolism genes reported the strongest associations between a SNP in *JMJ2DC* (aka *KDM4C*) (rs1340513) and ASD. (58) This same SNP was associated with ASD in female containing families in the Autism Genome Project Consortium study (9p24.1 (Zlr ¼ 3.21; m-P ¼ 0.0007). (59) In another analysis of this same sample, loss of function CNVs occurred in *RLN1* and *RLN2* in four cases and in *GLDC* in one case, and gain of function CNVS occurred in *RLN1* and *RLN2* in one case and in *KDM4C* in one case. (56) Nord et al. reported a paternally inherited deletion of part of *GLDC* in one ASD proband (chr9:6,560,979- 6,571,584). (60) Two brothers in the AGRE collection had a paternally inherited partial duplication of *GLDC/KDM4C* (Figure S17). (61) The Simons Simplex Collection also contains four families with partial duplications of *KDM4C* and *GLDC*. In 24 discordant severe autism sibling pairs, *GLDC* was differentially regulated in affecteds compared with siblings; 5/24 sib pairs showed up-regulation of at least 1.2-fold and 15 sib pairs showed down-regulation of at least 1.2-fold. (62) A breakpoint within the *KDM4C* gene was found in a patient

with ASD and gonadal dysgenesis. (63) Both the AGRE and the Simons Simplex Collections contain families in which probands have CNVs involving *GLDC* and *KDM4C*.

Intellectual Disability (ID)/Pervasive Developmental Delay (PDD)

Girirajan et al. reported novel overlapping deletions (3.5 Mbp and 9 Mbp) on chromosome 9p24 in two unrelated individuals with clinical features of ID and PDD-Not Otherwise Specified. (64) One of the two deletions included *GLDC, UHRF2, KDM4C, IL33, RANBP6, RLN1, RLN2, c9orf46, CD274, PDCD1LG2*, KIAA1432, *ERMP1*, *MLANA*, *KIAA2026, and TP52L3.* They also reported a paternally inherited deletion in a dyslexic that included all of *GLDC* and UHRF2 and part of *KDM4C* (see supplementary figure 2 of (64)). Yamamoto et al. reported that that one patient with ID and complex partial epilepsy had a deletion of *NARG2* and *RORA* on 15q21.3-q22.2 and a 1.6 Mb dup in 9p24.1 (5,420,412-7,029,245) that included all of *GLDC, UHRF2, RANBP6, IL33, KIAA2026,* and most of *KDM4C*. (65)

Other

Girirajan et al. reported a a paternally inherited deletion in a dyslexic that included all of *GLDC* and UHRF2 and part of *KDM4C.* (64) An 8 Mb *de novo* deletion on 9p, including all of the genes in the 9p24.1 region in family 611, was reported in a proband with a developmental disability. (66) Martinez-Jacobo et al. presented a case report of trisomy 9p24.3-9q21.11 involving a 69 Mb duplicated segment that included duplication of *GLDC* and *KDM4C* in a patient with multiple psychotic episodes and plus multiple dysmorphologies. (67) See also (11).

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Table S1: Double-Blind Exposure to Glycine – Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3	9	
1	3	3	Tuesday	4	12	
1	4	4	Wednesday	5	15	
1	5	5	Thursday	6	18	
1	6	6	Friday	7	21	
1	7	7	Saturday	8	24	
2	1	8	Sunday	9	27	
2	2	9	Monday	10	30	
2	3	10	Tuesday	12	36	
2	4	11	Wednesday	14	42	
2	5	12	Thursday	16	48	
2	6	13	Friday	18	54	
2	7	14	Saturday	20	60	
3	1	15	Sunday	22	66	
3	2	16	Monday	24	72	
3	3	17	Tuesday	25.3	76	
3	4	18	Wednesday	25.3	76	
3	5	19	Thursday	25.3	76	
3	6	20	Friday	0	0	Vomiting/diarrhea after breakfast dose; all other doses for day held
3	7	21	Saturday	0	0	All doses held
4	1	22	Sunday	20	40	2 doses (lunch and dinner)
4	2	23	Monday	20	60	
4	3	24	Tuesday	20	60	
4	4	25	Wednesday	20	60	
4	5	26	Thursday	20	60	
4	6	27	Friday	20	40	Forgot lunch dose
4	7	28	Saturday	21.33	64	
5	1	29	Sunday	21.33	64	
5	2	30	Monday	21.33	64	

Table S1: Double-Blind Exposure to Glycine – Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
5	3	31	Tuesday	21.33	64	
5	4	32	Wednesday	21.33	64	
5	5	33	Thursday	21.33	64	
5	6	34	Friday	21.33	64	
5	7	35	Saturday	21.33	64	
6	1	36	Sunday	25.3/21.33 BID	68	Accidentally took full dose at breakfast
6	2	37	Monday	25.3	76	
6	3	38	Tuesday	25.3	76	
6	4	39	Wednesday	25.3	76	
6	5	40	Thursday	25.3	76	
6	6	41	Friday	25.3	76	
6	7	42	Saturday	25.3	76	

Table S2: Double-Blind Exposure to Placebo - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3	9	
1	3	3	Tuesday	4	12	
1	4	4	Wednesday	5	15	
1	5	5	Thursday	6	18	
1	6	6	Friday	7	21	
1	7	7	Saturday	8	24	
2	1	8	Sunday	9	27	
2	2	9	Monday	10	20	Missed dinner dose
2	3	10	Tuesday	12	36	
2	4	11	Wednesday	14	42	
2	5	12	Thursday	16	48	
2	6	13	Friday	18	54	
2	7	14	Saturday	20	60	
3	1	15	Sunday	22	66	
3	2	16	Monday	24.2	72.7	
3	3	17	Tuesday	24.2	72.7	
3	4	18	Wednesday	24.2	72.7	
3	5	19	Thursday	24.2	48.4	Missed dinner dose
3	6	20	Friday	24.2	72.7	
3	7	21	Saturday	24.2	72.7	
4	1	22	Sunday	24.2	72.7	
4	2	23	Monday	24.2	72.7	

Table S2: Double-Blind Exposure to Placebo - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
4	3	24	Tuesday	24.2	72.7	
4	4	25	Wednesday	24.2	72.7	
4	5	26	Thursday	24.2	72.7	
4	6	27	Friday	24.2	72.7	
4	7	28	Saturday	24.2	72.7	
5	1	29	Sunday	24.2	72.7	
5	2	30	Monday	24.2	48.4	Missed dinner dose
5	3	31	Tuesday	24.2	72.7	
5	4	32	Wednesday	24.2	72.7	
5	5	33	Thursday	24.2	72.7	
5	6	34	Friday	24.2	72.7	
5	7	35	Saturday	24.2	72.7	
6	1	36	Sunday	24.2	72.7	
6	2	37	Monday	24.2	72.7	
6	3	38	Tuesday	24.2	72.7	
6	4	39	Wednesday	24.2	72.7	
6	5	40	Thursday	24.2	48.4	Missed dinner dose
6	6	41	Friday	24.2	72.7	
6	7	42	Saturday	24.2	72.7	

Table S3: Open-Label Exposure to Glycine – Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3.3	10	
1	3	3	Tuesday	4.7	14	
1	4	4	Wednesday	6	18	
1	5	5	Thursday	7.3	22	
1	6	6	Friday	8.7	26	
1	7	7	Saturday	10	30	
2	1	8	Sunday	11.3	34	
2	2	9	Monday	12.7	38	
2	3	10	Tuesday	14	42	
2	4	11	Wednesday	15.3	46	
2	5	12	Thursday	16.7	50	
2	6	13	Friday	18	54	
2	7	14	Saturday	19.3	58	
3	1	15	Sunday	20.7	62	
3	2	16	Monday	22	66	
3	3	17	Tuesday	23.3	70	
3	4	18	Wednesday	23.9	71.6	
3	5	19	Thursday	23.9	71.6	
3	6	20	Friday	23.9	71.6	
3	7	21	Saturday	23.9	71.6	
4	1	22	Sunday	23.9	71.6	
4	2	23	Monday	23.3	71.6	

Table S3: Open-Label Exposure to Glycine – Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
4	3	24	Tuesday	23.9	71.6	
4	4	25	Wednesday	23.9	71.6	
4	5	26	Thursday	23.9	23.9/22; total of 45.9g	Lunch dose held due to nausea; dinner dose reduced to 22 g
4	6	27	Friday	20.7	62	Nausea after dinner dose on day 5 of week 4; dose lowered to 20.7 g TID as of breakfast dose
4	7	28	Saturday	20.7	62	
5	1	29	Sunday	20.7	62	
5	2	30	Monday	20.7	62	
5	3	31	Tuesday	20.7	62	
5	4	32	Wednesday	20.7	62	
5	5	33	Thursday	20.7	62	
5	6	34	Friday	20.7	41.3	1 missed dose
5	7	35	Saturday	20.7	62	
6	1	36	Sunday	20.7	62	
6	2	37	Monday	20.7	62	
6	3	38	Tuesday	20.7	62	
6	4	39	Wednesday	20.7	62	
6	5	40	Thursday	20.7	62	
6	6	41	Friday	20.7x2; 23.9	65.3	forgot to reduce lunch dose
6	7	42	Saturday	20.7	62	

Table S4: Double-Blind Exposure to Placebo - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3	9	
1	3	3	Tuesday	4	12	
1	4	4	Wednesday	5	15	
1	5	5	Thursday	6	18	
1	6	6	Friday	7	21	
1	7	7	Saturday	8	24	
2	1	8	Sunday	9	27	
2	2	9	Monday	10	30	
2	3	10	Tuesday	12	36	
2	4	11	Wednesday	14	42	
2	5	12	Thursday	16	48	
2	6	13	Friday	18	54	
2	7	14	Saturday	20	60	
3	1	15	Sunday	22	66	
3	2	16	Monday	24	72	
3	3	17	Tuesday	26	78	
3	4	18	Wednesday	27.7	83	
3	5	19	Thursday	27.7	83	
3	6	20	Friday	27.7	83	
3	7	21	Saturday	27.7	83	
4	1	22	Sunday	27.7	83	
4	2	23	Monday	27.7	83	

Table S4: Double-Blind Exposure to Placebo - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
4	3	24	Tuesday	27.7	83	
4	4	25	Wednesday	27.7	83	
4	5	26	Thursday	27.7	83	
4	6	27	Friday	27.7	83	
4	7	28	Saturday	27.7	83	
5	1	29	Sunday	27.7	83	
5	2	30	Monday	27.7	83	
5	3	31	Tuesday	27.7	83	
5	4	32	Wednesday	27.7	83	
5	5	33	Thursday	27.7	83	
5	6	34	Friday	27.7	83	
5	7	35	Saturday	27.7	83	
6	1	36	Sunday	27.7	83	
6	2	37	Monday	27.7	83	
6	3	38	Tuesday	27.7	83	
6	4	39	Wednesday	27.7	83	
6	5	40	Thursday	27.7	83	
6	6	41	Friday	27.7	83	
6	7	42	Saturday	27.7	83	

Table S5: Double-Blind Exposure to Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3	9	
1	3	3	Tuesday	4	12	
1	4	4	Wednesday	5	15	
1	5	5	Thursday	6	18	
1	6	6	Friday	7	21	
1	7	7	Saturday	8	24	
2	1	8	Sunday	9	27	
2	2	9	Monday	10	30	
2	3	10	Tuesday	12	36	
2	4	11	Wednesday	14	42	
2	5	12	Thursday	16	48	
2	6	13	Friday	18	36	Vomited lunch dose
2	7	14	Saturday	20	60	
3	1	15	Sunday	22	66	
3	2	16	Monday	24	72	
3	3	17	Tuesday	26.5	79.6	
3	4	18	Wednesday	26.5	79.6	
3	5	19	Thursday	26.5/20	46.5*	26.5 breakfast; subject skipped lunch dose as instructed because of concern about possible exacerbation of psychotic symptoms; dinner dose reduced to 20 g*

Table S5: Double-Blind Exposure to Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
3	6	20	Friday	20	60	
3	7	21	Saturday	20	60	
4	1	22	Sunday	20	60	
4	2	23	Monday	20	60	
4	3	24	Tuesday	22	66	
4	4	25	Wednesday	22	66	
4	5	26	Thursday	24	72	
4	6	27	Friday	24	72	
4	7	28	Saturday	26.5	79.6	
5	1	29	Sunday	26.5	79.6	
5	2	30	Monday	26.5/24	24	Vomited after breakfast dose; held lunch; dinner 24 g total
5	3	31	Tuesday	24	72	
5	4	32	Wednesday	24	72	
5	5	33	Thursday	24 BID; 26.5	74.5	
5	6	34	Friday	24 BID; 26.5	48	Vomited after dinner dose; 48 g total
5	7	35	Saturday	24 TID	72	
6	1	36	Sunday	24 TID	72	
6	2	37	Monday	24 TID	72	
6	3	38	Tuesday	24 TID	72	
6	4	39	Wednesday	24 TID	72	
6	5	40	Thursday	24 BID/22	46	Vomited after lunch dose

Table S5: Double-Blind Exposure to Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
6	6	41	Friday	22 TID	66	
6	7	42	Saturday	22 TID	66	

* dose reduced because a family member thought subject was becoming more psychotic.

Table S6: Open-Label Exposure to Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	2	6	
1	2	2	Monday	3.3	10	
1	3	3	Tuesday	4.7	14	
1	4	4	Wednesday	6	18	
1	5	5	Thursday	7.3	22	
1	6	6	Friday	8.7	26	
1	7	7	Saturday	10	30	
2	1	8	Sunday	11.3	34	
2	2	9	Monday	12.7	38	
2	3	10	Tuesday	14	42	
2	4	11	Wednesday	15.3	46	
2	5	12	Thursday	16.7	50	
2	6	13	Friday	18	54	
2	7	14	Saturday	19.3	58	
3	1	15	Sunday	20.7	62	
3	2	16	Monday	22	66	
3	3	17	Tuesday	23.3	70	
3	4	18	Wednesday	24.7	74	
3	5	19	Thursday	26	78/52	Vomited after dinner dose – total intake 52g
3	6	20	Friday	27.3	81.8	
3	7	21	Saturday	27.3	81.8	Nausea after dinner dose

Table S6: Open-Label Exposure to Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
4	1	22	Sunday	27.3	66	Dose reduced to 22 g TID as of breakfast dose
4	2	23	Monday	22	66	
4	3	24	Tuesday	22	66	
4	4	25	Wednesday	22	66	
4	5	26	Thursday	22	66	
4	6	27	Friday	22	66	
4	7	28	Saturday	22	66	
5	1	29	Sunday	22	66	
5	2	30	Monday	22	66	
5	3	31	Tuesday	22	66	
5	4	32	Wednesday	22	66	
5	5	33	Thursday	22	66	
5	6	34	Friday	22	66	
5	7	35	Saturday	22	66	
6	1	36	Sunday	22	66	
6	2	37	Monday	22	66	
6	3	38	Tuesday	22	66	
6	4	39	Wednesday	22	66	
6	5	40	Thursday	22	66	
6	6	41	Friday	22	66	
6	7	42	Saturday	22	66	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	1.8	5.4	
1	2	2	Monday	3	9	
1	3	3	Tuesday	5	15	
1	4	4	Wednesday	6.1	18.3	
1	5	5	Thursday	6.8	20.4	
1	6	6	Friday	8	24	
1	7	7	Saturday	10	30	
2	1	8	Sunday	11.1	33.3	
2	2	9	Monday	11.8	35.4	
2	3	10	Tuesday	13	39	
2	4	11	Wednesday	14.1	42.3	
2	5	12	Thursday	15.4	46.2	
2	6	13	Friday	16	48	
2	7	14	Saturday	18	54	
3	1	15	Sunday	19.1	57.3	
3	2	16	Monday	19.8	59.4	
3	3	17	Tuesday	21	63	
3	4	18	Wednesday	21.6	64.8	21.6 TID Nausea
3	5	19	Thursday	18	54	Reduce dose to 18 TID
3	6	20	Friday	18	54	
3	7	21	Saturday	18	54	
4	1	22	Sunday	18	54	
4	2	23	Monday	18	54	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
4	3	24	Tuesday	18	36	18 BID – threw up at HS - migraine
4	4	25	Wednesday	18	36	18 BID – skipped breakfast dose
4	5	26	Thursday	18	54	
4	6	27	Friday	18	54	
4	7	28	Saturday	18	54	
5	1	29	Sunday	18	54	
5	2	30	Monday	18	36	Missed dinner dose
5	3	31	Tuesday	18	54	
5	4	32	Wednesday	18	54	
5	5	33	Thursday	18	54	
5	6	34	Friday	18	36	Missed dinner dose
5	7	35	Saturday	18	54	
6	1	36	Sunday	18	36	Missed dinner dose
6	2	37	Monday	18	54	
6	3	38	Tuesday	18	36	Missed dinner dose
6	4	39	Wednesday	18	36	Missed dinner dose
6	5	40	Thursday	18	54	
6	6	41	Friday	18	54	
6	7	42	Saturday	18	54	
7	1	43	Sunday	18	36	Missed dinner dose
7	2	44	Monday	18	54	
7	3	45	Tuesday	18	54	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
7	4	46	Wednesday	18	54	
7	5	47	Thursday	18	36	Missed dinner dose
7	6	48	Friday	18	54	
7	7	49	Saturday	18	54	
8	1	50	Sunday	18	54	
8	2	51	Monday	18	54	
8	3	52	Tuesday	18	54	
8	4	53	Wednesday	18	36	Missed dinner dose
8	5	54	Thursday	18	54	
8	6	55	Friday	18	54	
8	7	56	Saturday	18	54	
9	1	57	Sunday	18	54	
9	2	58	Monday	18	54	
9	3	59	Tuesday	18	36	Missed dinner dose
9	4	60	Wednesday	18	54	
9	5	61	Thursday	18	54	
9	6	62	Friday	18	54	
9	7	63	Saturday	18	54	
10	1	64	Sunday	18	54	
10	2	65	Monday	18	54	
10	3	66	Tuesday	18	54	
10	4	67	Wednesday	18	54	
10	5	68	Thursday	18	54	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
10	6	69	Friday	18	54	
10	7	70	Saturday	18	36	Missed dinner dose
11	1	71	Sunday	18	54	
11	2	72	Monday	18	36	Missed lunch dose
11	3	73	Tuesday	18	27	Missed lunch and half of dinner
11	4	74	Wednesday	18	36	Missed dinner dose
11	5	75	Thursday	18	54	
11	6	76	Friday	18	54	
11	7	77	Saturday	18	36	Missed dinner dose
12	1	78	Sunday	18	54	
12	2	79	Monday	18	54	
12	3	80	Tuesday	18	36	Missed dinner dose
12	4	81	Wednesday	18	54	
12	5	82	Thursday	18	54	
12	6	83	Friday	18	54	
12	7	84	Saturday	18	54	
13	1	85	Sunday	18	54	
13	2	86	Monday	18	54	
13	3	87	Tuesday	18	36	Missed lunch dose
13	4	88	Wednesday	18	54	
13	5	89	Thursday	18	54	
13	6	90	Friday	18	54	
13	7	91	Saturday	18	36	Missed dinner dose

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
14	1	92	Sunday	18	36	Missed lunch dose
14	2	93	Monday	18	54	
14	3	94	Tuesday	18	54	
14	4	95	Wednesday	18	36	Missed lunch dose
14	5	96	Thursday	18	36	Missed lunch dose
14	6	97	Friday	18	54	
14	7	98	Saturday	18	36	Missed lunch dose
15	1	99	Sunday	18	36	Missed dinner dose
15	2	100	Monday	18	36	Missed dinner dose
15	3	101	Tuesday	18	36	Missed dinner dose
15	4	102	Wednesday	18	36	Missed breakfast dose
15	5	103	Thursday	18	36	Missed dinner dose
15	6	104	Friday	18	36	Missed dinner dose
15	7	105	Saturday	18	36	Missed dinner dose
16	1	106	Sunday	18	18	Missed lunch/dinner doses
16	2	107	Monday	18	18	Missed breakfast/lunch doses
16	3	108	Tuesday	0	0	Missed all doses
16	4	109	Wednesday	0	0	Missed all doses
16	5	110	Thursday	18	18	Missed breakfast/lunch doses

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
16	6	111	Friday	18	18	Missed breakfast/dinner doses
16	7	112	Saturday	0	0	Stopped
17	1	113	Sunday	0	0	Stopped
17	2	114	Monday	0	0	Stopped
17	3	115	Tuesday	0	0	Stopped
17	4	116	Wednesday	0	0	Stopped
17	5	117	Thursday	0	0	Stopped
17	6	118	Friday	0	0	Stopped
17	7	119	Saturday	0	0	Stopped
18	1	120	Sunday	0	0	Stopped
18	2	121	Monday	0	0	Stopped
18	3	122	Tuesday	0	0	Stopped
18	4	123	Wednesday	0	0	Stopped
18	5	124	Thursday	0	0	Stopped
18	6	125	Friday	0	0	Stopped
18	7	126	Saturday	0	0	Stopped
19	1	127	Sunday	0	0	Stopped
19	2	128	Monday	0	0	Stopped
19	3	129	Tuesday	0	0	Stopped
19	4	130	Wednesday	0	0	Stopped
19	5	131	Thursday	0	0	Stopped
19	6	132	Friday	0	0	Stopped

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
19	7	133	Saturday	0	0	Stopped
20	1	134	Sunday	0	0	Stopped
20	2	135	Monday	0	0	Stopped
20	3	136	Tuesday	0	0	Stopped
20	4	137	Wednesday	0	0	Stopped
20	5	138	Thursday	0	0	Stopped
20	6	139	Friday	0	0	Stopped
20	7	140	Saturday	0	0	Stopped
21	1	141	Sunday	0	0	Stopped
21	2	142	Monday	0	0	Stopped
21	3	143	Tuesday	0	0	Stopped
21	4	144	Wednesday	0	0	Stopped
21	5	145	Thursday	0	0	Stopped
21	6	146	Friday	0	0	Stopped
21	7	147	Saturday	0	0	Stopped
22	1	148	Sunday	0	0	Stopped
22	2	149	Monday	0	0	Stopped
22	3	150	Tuesday	0	0	Stopped
22	4	151	Wednesday	0	0	Stopped
22	5	152	Thursday	0	0	Stopped
22	6	153	Friday	0	0	Stopped
22	7	154	Saturday	0	0	Stopped
23	1	155	Sunday	0	0	Stopped

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
23	2	156	Monday	0	0	Stopped
23	3	157	Tuesday	0	0	Stopped
23	4	158	Wednesday	0	0	Stopped
23	5	159	Thursday	0	0	Stopped
23	6	160	Friday	0	0	Stopped
23	7	161	Saturday	0	0	Stopped
24	1	162	Sunday	0	0	Stopped
24	2	163	Monday	0	0	Stopped
24	3	164	Tuesday	0	0	Stopped
24	4	165	Wednesday	0	0	Stopped
24	5	166	Thursday	0	0	Stopped
24	6	167	Friday	0	0	Stopped
24	7	168	Saturday	0	0	Stopped
25	1	169	Sunday	0	0	Stopped
25	2	170	Monday	0	0	Stopped
25	3	171	Tuesday	0	0	Stopped
25	4	172	Wednesday	0	0	Stopped
25	5	173	Thursday	0	0	Stopped
25	6	174	Friday	0	0	Stopped
25	7	175	Saturday	0	0	Stopped
26	1	176	Sunday	0	0	Stopped
26	2	177	Monday	1.8	3.6	Restarts
26	3	178	Tuesday	3	9	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
26	4	179	Wednesday	5	10	Missed dinner dose
26	5	180	Thursday	5	15	
26	6	181	Friday	5	15	
26	7	182	Saturday	5	15	
27	1	183	Sunday	10	30	
27	2	184	Monday	10	30	
27	3	185	Tuesday	10	30	
27	4	186	Wednesday	10	30	
27	5	187	Thursday	13	39	
27	6	188	Friday	13	39	
27	7	189	Saturday	13	39	
28	1	190	Sunday	13	39	
28	2	191	Monday	13	39	
28	3	192	Tuesday	13	39	
28	4	193	Wednesday	13	39	
28	5	194	Thursday	13	39	
28	6	195	Friday	13	39	
28	7	196	Saturday	13	39	
29	1	197	Sunday	13	39	
29	2	198	Monday	13	39	
29	3	199	Tuesday	13	39	
29	4	200	Wednesday	13	39	
29	5	201	Thursday	13	39	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
29	6	202	Friday	13	39	
29	7	203	Saturday	13	26	Missed dinner dose
30	1	204	Sunday	13	39	
30	2	205	Monday	13	39	
30	3	206	Tuesday	13	39	
30	4	207	Wednesday	13	39	
30	5	208	Thursday	13	39	
30	6	209	Friday	13	39	
30	7	210	Saturday	13	26	Missed dinner dose
31	1	211	Sunday	13	39	
31	2	212	Monday	13	39	
31	3	213	Tuesday	14.1	42.3	
31	4	214	Wednesday	13	39	
31	5	215	Thursday	0	0	Missed all doses
31	6	216	Friday	0	0	Missed all doses
31	7	217	Saturday	0	0	Missed all doses
32	1	218	Sunday	3	9	
32	2	219	Monday	5	15	
32	3	220	Tuesday	6.1	18.3	
32	4	221	Wednesday	6.8	20.4	
32	5	222	Thursday	10	30	
32	6	223	Friday	10	30	
32	7	224	Saturday	10	30	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
33	1	225	Sunday	10	20	Missed lunch dose
33	2	226	Monday	10	20	Missed dinner dose
33	3	227	Tuesday	10	20	Missed dinner dose
33	4	228	Wednesday	10	30	
33	5	229	Thursday	10	30	
33	6	230	Friday	10	30	
33	7	231	Saturday	10	30	
34	1	232	Sunday	10	20	Missed dinner dose
34	2	233	Monday	10	30	
34	3	234	Tuesday	10	30	
34	4	235	Wednesday	10	10	Missed lunch and dinner doses
34	5	236	Thursday	10	30	
34	6	237	Friday	0	0	Missed all doses
34	7	238	Saturday	10	20	Missed lunch dose
35	1	239	Sunday	10	20	Missed dinner dose
35	2	240	Monday	10	20	Missed dinner dose
35	3	241	Tuesday	10	30	
35	4	242	Wednesday	10	20	Missed dinner dose
35	5	243	Thursday	10	30	
35	6	244	Friday	10	30	
35	7	245	Saturday	10	30	
36	1	246	Sunday	10	30	
36	2	247	Monday	10 BID + 5	25	Reduce dinner

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
						dose to 5 g
36	3	248	Tuesday	10 BID + 5	25	
36	4	249	Wednesday	10 BID + 5	25	
36	5	250	Thursday	10 BID + 5	25	
36	6	251	Friday	10 BID + 5	25	
36	7	252	Saturday	10 BID + 5	25	
37	1	253	Sunday	10 BID	20	Missed dinner dose
37	2	254	Monday	10 BID	20	Missed dinner dose
37	3	255	Tuesday	10 BID + 5	25	
37	4	256	Wednesday	10 BID + 5	25	
37	5	257	Thursday	10 BID + 5	25	
37	6	258	Friday	10 BID + 5	25	
37	7	259	Saturday	10 BID + 5	25	
38	1	260	Sunday	10 BID + 5	25	
38	2	261	Monday	10 BID + 5	25	
38	3	262	Tuesday	10 BID + 5	25	
38	4	263	Wednesday	10 BID + 5	25	
38	5	264	Thursday	10 BID + 5	25	
38	6	265	Friday	10 BID + 5	25	
38	7	266	Saturday	10 BID + 5	25	
39	1	267	Sunday	10 BID + 5	25	
39	2	268	Monday	10 BID + 5	25	
39	3	269	Tuesday	10+5	15	Missed lunch dose

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
39	4	270	Wednesday	10 BID + 5	25	
39	5	271	Thursday	10 BID + 5	25	
39	6	272	Friday	10 BID + 5	25	
39	7	273	Saturday	10 BID + 5	25	
40	1	274	Sunday	10+5	15	Missed lunch dose
40	2	275	Monday	10+5	15	Missed lunch dose
40	3	276	Tuesday	10	10	Missed lunch and dinner doses
40	4	277	Wednesday	10 BID + 5	25	
40	5	278	Thursday	10 BID + 5	25	
40	6	279	Friday	10 BID + 5	25	
40	7	280	Saturday	10 BID + 5	25	
41	1	281	Sunday	10 BID + 5	25	
41	2	282	Monday	10 BID + 5	25	
41	3	283	Tuesday	10 BID + 5	25	
41	4	284	Wednesday	10 BID + 5	25	
41	5	285	Thursday	10 BID + 5	25	
41	6	286	Friday	10 BID + 5	25	
41	7	287	Saturday	10 BID	20	Missed dinner dose
42	1	288	Sunday	10 BID + 5	25	
42	2	289	Monday	10 BID + 5	25	
42	3	290	Tuesday	10 BID + 5	25	
42	4	291	Wednesday	10 BID + 5	25	
42	5	292	Thursday	10 BID + 5	25	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
42	6	293	Friday	10 BID + 5	25	
42	7	294	Saturday	10 BID + 5	25	
43	1	295	Sunday	10 BID + 5	25	
43	2	296	Monday	10 +5	15	Missed lunch dose
43	3	297	Tuesday	10 BID + 5	25	
43	4	298	Wednesday	10 BID + 5	25	
43	5	299	Thursday	10 BID + 5	25	
43	6	300	Friday	10 BID + 5	25	
43	7	301	Saturday	10 BID + 5	25	
44	1	302	Sunday	10 BID + 5	25	
44	2	303	Monday	10 BID + 5	25	
44	3	304	Tuesday	10 BID + 5	25	
44	4	305	Wednesday	10 BID + 5	25	
44	5	306	Thursday	10 BID + 5	25	
44	6	307	Friday	10 BID + 5	25	
44	7	308	Saturday	10 BID + 5	25	
45	1	309	Sunday	10 BID + 5	25	
45	2	310	Monday	10 BID + 5	25	
45	3	311	Tuesday	10 BID + 5	25	
45	4	312	Wednesday	10 BID + 5	25	
45	5	313	Thursday	10 BID + 5	25	
45	6	314	Friday	10 BID + 5	25	
45	7	315	Saturday	10 BID + 5	25	

Table S7. Open-Label Exposure to Chronic Glycine - Subject 3363: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
46	1	316	Sunday	10 BID + 5	25	
46	2	317	Monday	10 BID + 5	25	
46	3	318	Tuesday	10 BID + 5	25	
46	4	319	Wednesday	10 BID + 5	25	
46	5	320	Thursday	0	0	Missed all doses
46	6	321	Friday	0	0	Missed all doses
46	7	322	Saturday	10+5	15	Missed breakfast
47	1	323	Sunday	10 BID + 5	25	
47	2	324	Monday	10 BID + 5	25	
47	3	325	Tuesday	10 BID + 5	25	
47	4	326	Wednesday	10 BID + 5	25	
47	5	327	Thursday	10	10	Breakfast only

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
1	1	1	Sunday	1.8	5.4	
1	2	2	Monday	3	9	
1	3	3	Tuesday	5	15	
1	4	4	Wednesday	6.1	18.3	
1	5	5	Thursday	6.8	20.4	
1	6	6	Friday	8	24	
1	7	7	Saturday	10	30	
2	1	8	Sunday	11.1	33.3	
2	2	9	Monday	11.8	35.4	
2	3	10	Tuesday	13	39	
2	4	11	Wednesday	14.1	42.3	
2	5	12	Thursday	15.4	46.2	Nauseated but took salt tablet and felt ok.
2	6	13	Friday	16	31.4	Acutely nauseated within 45 minutes of breakfast dose. Took salt tablet and it did not help. Holding lunch dose. If better by dinner, take 15.4.
2	7	14	Saturday	16	48	
3	1	15	Sunday	18	54	
3	2	16	Monday	19.1	57.3	
3	3	17	Tuesday	19.8	59.4	
3	4	18	Wednesday	21	63	Stops increasing dose here

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
3	5	19	Thursday	21	63	
3	6	20	Friday	21	63	
3	7	21	Saturday	21	63	
4	1	22	Sunday	21	63	
4	2	23	Monday	21	63	
4	3	24	Tuesday	21	63	
4	4	25	Wednesday	21	63	
4	5	26	Thursday	21	63	
4	6	27	Friday	21	63	
4	7	28	Saturday	21	63	
5	1	29	Sunday	21	63	
5	2	30	Monday	21	63	
5	3	31	Tuesday	21	63	
5	4	32	Wednesday	21	63	
5	5	33	Thursday	21	63	
5	6	34	Friday	21	63	
5	7	35	Saturday	21	63	
6	1	36	Sunday	21	63	
6	2	37	Monday	21	63	
6	3	38	Tuesday	21	63	
6	4	39	Wednesday	21	63	
6	5	40	Thursday	21	63	
6	6	41	Friday	21	63	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
6	7	42	Saturday	21	63	
7	1	43	Sunday	21	63	
7	2	44	Monday	21	63	
7	3	45	Tuesday	21	63	
7	4	46	Wednesday	21	63	
7	5	47	Thursday	21	63	
7	6	48	Friday	21	42	No dinner dose
7	7	49	Saturday	21	42	No dinner dose
8	1	50	Sunday	21	42	No dinner dose
8	2	51	Monday	21	42	No dinner dose
8	3	52	Tuesday	21	42	No dinner dose
8	4	53	Wednesday	21	42	No dinner dose
8	5	54	Thursday	18	36	Reduced dose to 18 g TID so can drink quicker without queasiness after dinner but see below – skipped most dinner doses until 10/3/2014
8	6	55	Friday	18	36	No dinner dose
8	7	56	Saturday	18	36	No dinner dose
9	1	57	Sunday	18	36	No dinner dose
9	2	58	Monday	18	36	No dinner dose
9	3	59	Tuesday	18	36	No dinner dose
9	4	60	Wednesday	18	36	No dinner dose
9	5	61	Thursday	18	36	No dinner dose

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
9	6	62	Friday	18	36	No dinner dose
9	7	63	Saturday	18	36	No dinner dose
10	1	64	Sunday	18	36	No dinner dose
10	2	65	Monday	18	36	No dinner dose
10	3	66	Tuesday	18	36	No dinner dose
10	4	67	Wednesday	18	36	No dinner dose
10	5	68	Thursday	18	36	No dinner dose
10	6	69	Friday	18	18	Took only one dose
10	7	70	Saturday	18	36	No dinner dose
11	1	71	Sunday	18	36	No dinner dose
11	2	72	Monday	18	36	No dinner dose
11	3	73	Tuesday	18	36	No dinner dose
11	4	74	Wednesday	18	36	Due to so many skipped doses take only 6 g at dinner – skipped dinner dose
11	5	75	Thursday	18	36	No dinner dose
11	6	76	Friday	18	36	No dinner dose
11	7	77	Saturday	18	36	No dinner dose
12	1	78	Sunday	18	36	No dinner dose
12	2	79	Monday	18	36	No dinner dose
12	3	80	Tuesday	18	36	No dinner dose
12	4	81	Wednesday	18	36	No dinner dose
12	5	82	Thursday	18	36	No dinner dose

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
12	6	83	Friday	18	36	No dinner dose
12	7	84	Saturday	18	36	No dinner dose
13	1	85	Sunday	18	36	No dinner dose
13	2	86	Monday	18	36	No dinner dose
13	3	87	Tuesday	18	36	No dinner dose
13	4	88	Wednesday	18	36	No dinner dose
13	5	89	Thursday	18	36	No dinner dose
13	6	90	Friday	18	36	No dinner dose
13	7	91	Saturday	18	36	No dinner dose
14	1	92	Sunday	18	36	No dinner dose
14	2	93	Monday	18	36	No dinner dose
14	3	94	Tuesday	18	36	No dinner dose
14	4	95	Wednesday	18	36	No dinner dose
14	5	96	Thursday	18	36	No dinner dose
14	6	97	Friday	18	36	No dinner dose
14	7	98	Saturday	18	36	No dinner dose
15	1	99	Sunday	18	36	No dinner dose
15	2	100	Monday	18	36	No dinner dose
15	3	101	Tuesday	18	36	No dinner dose
15	4	102	Wednesday	18	36	No dinner dose
15	5	103	Thursday	18	36	No dinner dose
15	6	104	Friday	18	36	No dinner dose
15	7	105	Saturday	18	36	No dinner dose

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
16	1	106	Sunday	18	27	Took 1.5 doses
16	2	107	Monday	18	27	Took 1.5 doses
16	3	108	Tuesday	18	27	Took 1.5 doses
16	4	109	Wednesday	18	18	Took only one dose
16	5	110	Thursday	18	18	Took only one dose
16	6	111	Friday	18	18	Took only one dose
16	7	112	Saturday	0	0	Stopped
17	1	113	Sunday	0	0	Stopped
17	2	114	Monday	0	0	Stopped
17	3	115	Tuesday	0	0	Stopped
17	4	116	Wednesday	0	0	Stopped
17	5	117	Thursday	0	0	Stopped
17	6	118	Friday	0	0	Stopped
17	7	119	Saturday	0	0	Stopped
18	1	120	Sunday	0	0	Stopped
18	2	121	Monday	0	0	Stopped
18	3	122	Tuesday	0	0	Stopped
18	4	123	Wednesday	0	0	Stopped
18	5	124	Thursday	0	0	Stopped
18	6	125	Friday	0	0	Stopped
18	7	126	Saturday	0	0	Stopped
19	1	127	Sunday	0	0	Stopped
19	2	128	Monday	0	0	Stopped

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
19	3	129	Tuesday	5	5	Re-starts glycine – one dose in evening
19	4	130	Wednesday	5	15	
19	5	131	Thursday	5	15	
19	6	132	Friday	5	10	Skipped one dose
19	7	133	Saturday	5	10	Skipped one dose
20	1	134	Sunday	5	15	
20	2	135	Monday	5	15	
20	3	136	Tuesday	6.1	18.3	
20	4	137	Wednesday	6.8	20.4	
20	5	138	Thursday	6.8	20.4	
20	6	139	Friday	6.8	20.4	
20	7	140	Saturday	6.8	20.4	
21	1	141	Sunday	6.8	20.4	
21	2	142	Monday	8	24	
21	3	143	Tuesday	8	24	
21	4	144	Wednesday	8	24	
21	5	145	Thursday	8	24	
21	6	146	Friday	8	24	
21	7	147	Saturday	8	24	
22	1	148	Sunday	10	30	
22	2	149	Monday	10	30	
22	3	150	Tuesday	10	30	
22	4	151	Wednesday	10	30	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
22	5	152	Thursday	10	30	
22	6	153	Friday	10	30	
22	7	154	Saturday	10	10	Missed 2 doses
23	1	155	Sunday	10	30	
23	2	156	Monday	10	30	
23	3	157	Tuesday	10	30	
23	4	158	Wednesday	10	30	
23	5	159	Thursday	10	30	
23	6	160	Friday	10	30	
23	7	161	Saturday	10	30	
24	1	162	Sunday	13	39	No side effects
24	2	163	Monday	13	39	
24	3	164	Tuesday	13	39	
24	4	165	Wednesday	13	39	
24	5	166	Thursday	13	39	
24	6	167	Friday	13	39	
24	7	168	Saturday	13	39	
25	1	169	Sunday	13	39	
25	2	170	Monday	13	39	
25	3	171	Tuesday	13	39	No side effects
25	4	172	Wednesday	13	39	
25	5	173	Thursday	13	39	
25	6	174	Friday	13	39	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
25	7	175	Saturday	13	39	
26	1	176	Sunday	13	39	
26	2	177	Monday	13	39	
26	3	178	Tuesday	13	39	No side effects
26	4	179	Wednesday	13	39	
26	5	180	Thursday	13	39	
26	6	181	Friday	13	39	
26	7	182	Saturday	13	39	
27	1	183	Sunday	13	39	
27	2	184	Monday	13	39	
27	3	185	Tuesday	13	39	
27	4	186	Wednesday	13	39	No side effects
27	5	187	Thursday	13	39	
27	6	188	Friday	13	39	
27	7	189	Saturday	13	39	
28	1	190	Sunday	13	39	
28	2	191	Monday	13	39	No side effects
28	3	192	Tuesday	13	39	
28	4	193	Wednesday	13	39	
28	5	194	Thursday	13	39	
28	6	195	Friday	13	39	
28	7	196	Saturday	13	39	
29	1	197	Sunday	13	39	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
29	2	198	Monday	13	39	
29	3	199	Tuesday	0	0	No doses
29	4	200	Wednesday	13	26	Missed one dose
29	5	201	Thursday	13	39	
29	6	202	Friday	13	39	
29	7	203	Saturday	13	39	
30	1	204	Sunday	13	39	
30	2	205	Monday	13	39	
30	3	206	Tuesday	13	39	
30	4	207	Wednesday	13	39	
30	5	208	Thursday	13	39	
30	6	209	Friday	13	39	
30	7	210	Saturday	13	39	
31	1	211	Sunday	13	39	
31	2	212	Monday	10	30	Loose stools
31	3	213	Tuesday	10	30	
31	4	214	Wednesday	10	30	
31	5	215	Thursday	10	30	
31	6	216	Friday	10	30	
31	7	217	Saturday	10	30	
32	1	218	Sunday	10	30	
32	2	219	Monday	10	30	
32	3	220	Tuesday	0	0	No doses

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
32	4	221	Wednesday	8	24	Loose stools
32	5	222	Thursday	8	24	
32	6	223	Friday	8	24	
32	7	224	Saturday	8	24	
33	1	225	Sunday	8	24	
33	2	226	Monday	8	24	
33	3	227	Tuesday	0	0	No doses
33	4	228	Wednesday	8	16	Missed one dose
33	5	229	Thursday	8	16	
33	6	230	Friday	8	16	
33	7	231	Saturday	8	16	
34	1	232	Sunday	8	16	Missed one dose
34	2	233	Monday	8	8	One dose
34	3	234	Tuesday	8	8	One dose
34	4	235	Wednesday	10	10	Diarrhea on second dose
34	5	236	Thursday	5	5	One dose
34	6	237	Friday	5	10	Two doses
34	7	238	Saturday	5	10	Two doses
35	1	239	Sunday	5	10	Two doses
35	2	240	Monday	5	5	Take only 5 g/d
35	3	241	Tuesday	5	5	Take only 5 g/d
35	4	242	Wednesday	5	5	Take only 5 g/d
35	5	243	Thursday	5	5	Take only 5 g/d

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
35	6	244	Friday	5	5	Take only 5 g/d
35	7	245	Saturday	5	5	Take only 5 g/d
36	1	246	Sunday	5	5	Take only 5 g/d
36	2	247	Monday	5	5	Take only 5 g/d
36	3	248	Tuesday	5	5	Take only 5 g/d
36	4	249	Wednesday	5	5	Take only 5 g/d
36	5	250	Thursday	5	5	Take only 5 g/d
36	6	251	Friday	5	5	Take only 5 g/d
36	7	252	Saturday	5	5	Take only 5 g/d
37	1	253	Sunday	5	5	Take only 5 g/d
37	2	254	Monday	5	5	Take only 5 g/d
37	3	255	Tuesday	5	5	Take only 5 g/d
37	4	256	Wednesday	5	5	Take only 5 g/d
37	5	257	Thursday	5	5	Take only 5 g/d
37	6	258	Friday	5	5	Take only 5 g/d
37	7	259	Saturday	5	5	Take only 5 g/d
38	1	260	Sunday	5	5	Take only 5 g/d
38	2	261	Monday	6.1	6.1	Increase to 6.1
38	3	262	Tuesday	6.1	6.1	
38	4	263	Wednesday	6.1	6.1	
38	5	264	Thursday	6.1	6.1	
38	6	265	Friday	6.1	6.1	
38	7	266	Saturday	6.1	6.1	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
39	1	267	Sunday	6.1	6.1	
39	2	268	Monday	6.1	6.1	
39	3	269	Tuesday	6.1	6.1	
39	4	270	Wednesday	6.1	6.1	
39	5	271	Thursday	0	0	Missed all
39	6	272	Friday	0	0	Missed all
39	7	273	Saturday	0	0	Missed all
40	1	274	Sunday	0	0	Loose stools
40	2	275	Monday	5	5	Loose stools
40	3	276	Tuesday	0	0	
40	4	277	Wednesday	0	0	
40	5	278	Thursday	5	5	Loose stools
40	6	279	Friday	5	5	
40	7	280	Saturday	5	5	
41	1	281	Sunday	5	5	
41	2	282	Monday	5	5	
41	3	283	Tuesday	5	5	
41	4	284	Wednesday	5	5	
41	5	285	Thursday	5	5	
41	6	286	Friday	5	5	
41	7	287	Saturday	5	5	
42	1	288	Sunday	5	5	
42	2	289	Monday	5	5	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
42	3	290	Tuesday	5	5	
42	4	291	Wednesday	5	5	
42	5	292	Thursday	5	5	
42	6	293	Friday	5	5	
42	7	294	Saturday	5	5	
43	1	295	Sunday	5	5	
43	2	296	Monday	5	5	
43	3	297	Tuesday	5	5	
43	4	298	Wednesday	5	5	
43	5	299	Thursday	5	5	
43	6	300	Friday	5	5	
43	7	301	Saturday	5	5	
44	1	302	Sunday	5	5	
44	2	303	Monday	5	5	
44	3	304	Tuesday	5	5	
44	4	305	Wednesday	5	5	
44	5	306	Thursday	5	5	
44	6	307	Friday	5	5	
44	7	308	Saturday	5	5	
45	1	309	Sunday	0	0	No doses
45	2	310	Monday	0	0	No doses
45	3	311	Tuesday	5	5	
45	4	312	Wednesday	5	5	

Table S8. Open-Label Exposure to Chronic Glycine - Subject 5459: Actual Titration

Week	Day	Day (cumulative)	Day of Week	Dose (g) TID	Total Daily Dose (g)	Deviation from Scheduled Dose
45	5	313	Thursday	5	5	
45	6	314	Friday	0	0	Missed all doses
45	7	315	Saturday	0	0	Missed all doses
46	1	316	Sunday	0	0	Missed all doses
46	2	317	Monday	5	5	
46	3	318	Tuesday	5	5	
46	4	319	Wednesday	5	5	
46	5	320	Thursday	5	5	
46	6	321	Friday	5	5	
46	7	322	Saturday	5	5	
47	1	323	Sunday	5	5	
47	2	324	Monday	5	5	Last day of dosing

Table S1A. Double-Blind Exposure to Glycine - Subject 5459: Planned Titration

McLean Hospital Research Pharmacy

Dose Titration for Glycine/Palatinose 3:1 Mixture - Arm 1

("Palatinose 3:1 Mixture," also referred to "Palatinose," is the placebo for glycine)

Titration Schedule for subject #5459, Arm 1, is based on a weight of 209 lbs (95 kg).

Dose Titration: Start with 6 gm/day on day one and increase as noted below, until maintenance dose of 0.8 gm glycine/placebo per kg body weight (76 gm/day) is achieved.

Note: glycine/placebo is dosed TID

Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine/palatinose bottle (A) and then add water to the fill line indicated on the glycine/palatinose bottle (A). When mixed as instructed, the flavored Glycine/Patatinose solution results in a final glycine/palatinose concentration of 20% w/v (0.2 gm glycine/palatinose/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.

If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine/Palatinose Total Daily Dose (gm/day)	Glycine/Palatinose (gm/dose) (dosed TID)	Total Volume(mL)/Dose (dosed TID)
1	1	6	2	10
	2	9	3	15
	3	12	4	20
	4	15	5	25
	5	18	6	30
	6	21	7	35
	7	24	8	40
2	1	27	9	45
	2	30	10	50
	3	36	12	60
	4	42	14	70
	5	48	16	80
	6	54	18	90
	7	60	20	100
3	1	66	22	110
	2	72	24	120

Table S1A. Double-Blind Exposure to Glycine - Subject 5459: Planned Titration

Week 3, day 3 thru Week 6 day 7 (maintenance dose)	76	25.3	126.7

Table S2A. Double-Blind Exposure to Placebo - Subject 5459: Planned Titration

McLean Hospital Research Pharmacy

Dose Titration for Glycine/Palatinose 3:1 Mixture - Arm 2

("Palatinose 3:1 Mixture," also referred to "Palatinose," is the placebo for glycine)
Titration Schedule for subject #5459, Arm 2, is based on a weight of 200 lbs (90.9 kg).

Dose Titration: Start with 6 gm/day on week 9, day one, and increase as noted below, until maintenance dose of 0.8 gm glycine/placebo per kg body weight (72.7 gm/day) is achieved.

Note: glycine/placebo is dosed TID

Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine/palatinose bottle (A) and then add water to the fill line indicated on the glycine/palatinose bottle (A). When mixed as instructed, the flavored Glycine/Patatinose solution results in a final glycine/palatinose concentration of 20% w/v (0.2 gm glycine/palatinose/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.

If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine/Palatinose Total Daily Dose (gm/day)	Glycine/Palatinose (gm/dose) (dosed TID)	Total Volume(mL)/Dose (dosed TID)
1	1	6	2	10
	2	9	3	15
	3	12	4	20
	4	15	5	25
	5	18	6	30
	6	21	7	35
	7	24	8	40
2	1	27	9	45
	2	30	10	50
	3	36	12	60
	4	42	14	70
	5	48	16	80
	6	54	18	90
	7	60	20	100
3	1	66	22	110
Week 3 day 2 thru Week 6 day 7 (maintenance dose)		72.7	24.2	121

Table S3A. Open-Label Exposure to Glycine - Subject 5459: Planned Titration

McLean Hospital Research Pharmacy

Dose Titration for Glycine Powder and Flavoring Additives - Open Label Phase

Titration Schedule for subject #5459, Open Label Phase, is based on a weight of 197 lbs (89.5 kg).

Dose Titration: Start with 6 gm/day on week one, day one, and increase by 4 gm/day (different titration rate than the double-blind phase) until a maintenance dose of 0.8 gm glycine per kg body weight (71.6 gm/day) is achieved.
Note: glycine is dosed TID

Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine bottle (A) and then add water to the fill line indicated on the glycine bottle (A). When mixed as instructed, the flavored glycine solution results in a final glycine concentration of 20% w/v (0.2 gm glycine/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.
If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine Total Daily Dose gm/day	Glycine gm/dose (dosed TID)	Total Volume mL/Dose (dosed TID)
1	1	6	2	10
	2	10	3.3	16.5
	3	14	4.7	23.5
	4	18	6	30
	5	22	7.3	36.5
	6	26	8.7	43.5
	7	30	10	50
2	1	34	11.3	56.5
	2	38	12.7	63.5
	3	42	14	70
	4	46	15.3	76.5
	5	50	16.7	83.5
	6	54	18	90
	7	58	19.3	96.5
3	1	62	20.7	103.5
	2	66	22	110
	3	70	23.3	116.5
Week 3 day 4 thru Week 6 day 7 (maintenance dose)		71.6	23.9	119.5

Table S4A. Double-Blind Exposure to Placebo - Subject 3363: Planned Titration

McLean Hospital Research Pharmacy
Dose Titration for Glycine/Palatinose 3:1 Mixture - Arm 1

("Palatinose 3:1 Mixture," also referred to "Palatinose," is the placebo for glycine)
Titration Schedule for subject #3363, Arm 1, is based on a weight of 228 lbs (103.6 kg).
Dose Titration: Start with 6 gm/day on day one and increase as noted below, until maintenance dose of 0.8 gm glycine/placebo per kg body weight (83 gm/day) is achieved.
Note: glycine/placebo is dosed TID
Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine/palatinose bottle (A) and then add water to the fill line indicated on the glycine/palatinose bottle (A). When mixed as instructed, the flavored Glycine/Patatinose solution results in a final glycine/palatinose concentration of 20% w/v (0.2 gm glycine/palatinose/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.

If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine/Palatinose Total Daily Dose (gm/day)	Glycine/Palatinose (gm/dose) (dosed TID)	Total Volume(mL)/Dose (dosed TID)
1	1	6	2	10
	2	9	3	15
	3	12	4	20
	4	15	5	25
	5	18	6	30
	6	21	7	35
	7	24	8	40
2	1	27	9	45
	2	30	10	50
	3	36	12	60
	4	42	14	70
	5	48	16	80
	6	54	18	90
	7	60	20	100
3	1	66	22	110
	2	72	24	120
	3	78	26	130
Week 3, day 4 thru Week 6 day 7 (maintenance dose)		83	27.7	138.3

Table S5A. Double-Blind Exposure to Glycine - Subject 3363: Planned Titration

McLean Hospital Research Pharmacy

Dose Titration for Glycine/Palatinose 3:1 Mixture - Arm 2

("Palatinose 3:1 Mixture," also referred to "Palatinose," is the placebo for glycine)
Titration Schedule for subject #3363, Arm 2, is based on a weight of 219 lbs (99.5 kg).

Dose Titration: Start with 6 gm/day on week 11, day one, and increase as noted below, until maintenance dose of 0.8 gm glycine/placebo per kg body weight (79.6 gm/day) is achieved.

Note: glycine/placebo is dosed TID

Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine/palatinose bottle (A) and then add water to the fill line indicated on the glycine/palatinose bottle (A). When mixed as instructed, the flavored Glycine/Patatinose solution results in a final glycine/palatinose concentration of 20% w/v (0.2 gm glycine/palatinose/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.
If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine/Palatinose Total Daily Dose (gm/day)	Glycine/Palatinose (gm/dose) (dosed TID)	Total Volume (mL)/Dose (dosed TID)
1	1	6	2	10
	2	9	3	15
	3	12	4	20
	4	15	5	25
	5	18	6	30
	6	21	7	35
	7	24	8	40
2	1	27	9	45
	2	30	10	50
	3	36	12	60
	4	42	14	70
	5	48	16	80
	6	54	18	90
	7	60	20	100
3	1	66	22	110
	2	72	24	120
Week 3 day 3 thru Week 6 day 7 (maintenance dose)		79.6	26.5	132.5

Table S6A. Open-Label Exposure to Glycine - Subject 3363: Planned Titration

McLean Hospital Research Pharmacy

Dose Titration for Glycine Powder and Flavoring Additives - Open Label Phase

Titration Schedule for subject #3363, Open Label Phase, is based on a weight of 225 lbs (102.3 kg).

Dose Titration: Start with 6 gm/day on week one, day one, and increase by 4 gm/day (different titration rate than the double-blind phase) until a maintenance dose of 0.8 gm glycine per kg body weight (81.8 gm/day) is achieved.
Note: glycine is dosed TID

Reconstitution Directions: Subjects pour contents from flavoring bottle (B) into glycine bottle (A) and then add water to the fill line indicated on the glycine bottle (A). When mixed as instructed, the flavored glycine solution results in a final glycine concentration of 20% w/v (0.2 gm glycine/mL of solution). Volume contributed by the various powders has been factored into the calculation for the amount of water required to attain a 20% solution.
If a subject's dose needs to be changed for any reason, reconstitution directions remain the same. ***The volume to be administered will need to be adjusted***. Below is the titration schedule showing gm/dose and volume/dose.

Week #	Day #	Glycine Total Daily Dose gm/day	Glycine gm/dose (dosed TID)	Total Volume mL/Dose (dosed TID)
	1	6	2	10
	2	10	3.3	16.5
	3	14	4.7	23.5
1	4	18	6	30
	5	22	7.3	36.5
	6	26	8.7	43.5
	7	30	10	50
	1	34	11.3	56.5
	2	38	12.7	63.5
	3	42	14	70
2	4	46	15.3	76.5
	5	50	16.7	83.5
	6	54	18	90
	7	58	19.3	96.5
	1	62	20.7	103.5
	2	66	22	110
3	3	70	23.3	116.5
	4	74	24.7	123.5
	5	78	26	130
Week 3 day 6 thru Week 6 day 7 (maintenance dose)		81.8	27.3	136.5

Table S7A. Open-Label Exposure to Chronic Glycine - Subject 3363: Planned Titration

Investigator's Copy: Maintenance dose for Subject #3363 of 28.8 gm/dose (86.5 gm/day) based on body wt. of 238 lbs (108.1 kg).

Important Note:

- Glycine powder & distilled water are to be measured & mixed, making doses of Glycine 20% solution, which will be taken 3 times/day
- The ***Glycine powder*** must be ***loosened in its jar before*** it is measured (see instructions below)
- ***Glycine powder must be measured lightly with the measuring spoons provided. Do not pack the powder into the measuring spoons***
- The amount of Glycine powder/measuring spoon is specific for spoons filled lightly with loosened Glycine powder ***(not packed)***
- Measure distilled water with the graduated cylinder provided
- Do not mix Glycine solutions ahead of time. Prepare each dose at the time of use
- The total daily dose of Glycine will be increased by approx 4gm/day (**1.3 gm/dose**) to a maintenance dose of **0.8 gm glycine/kg** body wt

Instructions- Preparing Doses of Glycine 20% Solution

1. Check that the lid is secured on the jar of Glycine powder. Gently roll/rotate jar several times *to loosen the powder before measuring*
2. Refer to the titration schedule for HOW MANY & WHICH SIZE measuring spoons are needed to measure each dose of Glycine powder
3. Lightly fill the first measuring spoon with the Glycine powder (*do not pack powder into the spoon)*
4. Level the measuring spoon with a straight edge *over the jar*, so the excess powder falls back into the jar
5. Transfer the Glycine powder from the measuring spoon into the bottle provided
6. Measure additional spoonful(s) of Glycine Powder (per titration) until the full dose has been measured & placed in the bottle provided
7. Measure the amount of distilled water needed per dose using the graduated cylinder provided (see titration for amount of water/dose)
8. Pour the measured amount of water into the bottle containing the measured dose of Glycine powder
9. Cap bottle & shake for several minutes to dissolve to produce a 20% Glycine solution in the amount needed for the dose
10. Flavor solution to taste using the TrueCitrus® Lemon and Lime flavoring packets provided- Cap bottle & shake to dissolve
    (Note: For the plain TrueLemon and TrueLime flavors, 1 packet = 0.8 gm, which is approximately 1/4 teaspoonful)
11. Drink the entire dose slowly, over a 15 minute period

Table S7A. Open-Label Exposure to Chronic Glycine - Subject 3363: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID) # of Spoonfuls	X	Measuring Spoon Size	Glycine (Gm per Spoonful)	+	Water Amt to Add/ Dose (mL)	=	Glycine 20% Soln Final Volume/Dose (mL)
1	1	1.8	One	X	1/2 teaspoonful	(1.8 gm)	+	8 mL	=	9 mL
	2	3	One	X	3/4 teaspoonful	(3 gm)	+	13 mL	=	15 mL
	3	5	One	X	1 teaspoonful	(5 gm)	+	22 mL	=	25 mL
	4	6.1	One	X	1 teaspoonful	(5 gm)	+	27 mL	=	30.5 mL
			One	X	1/4 teaspoonful	(1.1 gm)				
	5	6.8	One	X	1 teaspoonful	(5 gm)	+	30 mL	=	34 mL
			One	X	1/2 teaspoonful	(1.8 gm)				
	6	8	One	X	1 teaspoonful	(5 gm)	+	35 mL	=	40 mL
			One	X	3/4 teaspoonful	(3 gm)				
	7	10	TWO	X	1 teaspoonful	(5 gm)	+	44 mL	=	50 mL
2	1	11.1	TWO	X	1 teaspoonful	(5 gm)	+	49 mL	=	55.5 mL
			One	X	1/4 teaspoonful	(1.1 gm)				
	2	11.8	TWO	X	1 teaspoonful	(5 gm)	+	52 mL	=	59 mL
			One	X	1/2 teaspoonful	(1.8 gm)				
	3	13	One	X	1 Tablespoon	(13 gm)	+	57 mL	=	65 mL
	4	14.1	One	X	1 Tablespoon	(13 gm)	+	62 mL	=	70.5 mL
			One	X	1/4 teaspoonful	(1.1 gm)				
	5	15.4	One	X	1 Tablespoon	(13 gm)	+	68 mL	=	77 mL
			One	X	1/2 teaspoonful	(1.8 gm)				
			One	X	1/8 teaspoonful	(0.6 gm)				
	6	16	One	X	1 Tablespoon	(13 gm)	+	71 mL	=	80 mL
			One	X	3/4 teaspoonful	(3 gm)				
	7	18	One	X	1 Tablespoon	(13 gm)	+	79 mL	=	90 mL
			One	X	1 teaspoonful	(5 gm)				

Table S7A. Open-Label Exposure to Chronic Glycine - Subject 3363: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID)				Glycine	+	Water Amt to Add/ Dose (mL)		=	Glycine 20% Soln Final Volume/Dose (mL)	
			# of Spoonfuls	X	Measuring Spoon Size		(Gm per Spoonful)						
3	1	19.1	One	X	1	Tablespoon	(13 gm)	+	84	mL	=	95.5	mL
			One	X	1	teaspoonful	(5 gm)						
			One	X	1/4	teaspoonful	(1.1 gm)						
	2	19.8	One	X	1	Tablespoon	(13 gm)	+	87	mL	=	99	mL
			One	X	1	teaspoonful	(5 gm)						
			One	X	1/2	teaspoonful	(1.8 gm)						
	3	21	One	X	1	Tablespoon	(13 gm)	+	93	mL	=	105	mL
			One	X	1	teaspoonful	(5 gm)						
			One	X	3/4	teaspoonful	(3 gm)						
	4	21.6	One	X	1	Tablespoon	(13 gm)	+	95	mL	=	108	mL
			One	X	1	teaspoonful	(5 gm)						
			One	X	3/4	teaspoonful	(3 gm)						
			One	X	1/8	teaspoonful	(0.6 gm)						
	5	23.6	One	X	1	Tablespoon	(13 gm)	+	104	mL	=	118	mL
			TWO	X	1	teaspoonful	(5 gm)						
			One	X	1/8	teaspoonful	(0.6 gm)						
	6	24.1	One	X	1	Tablespoon	(13 gm)	+	106	mL	=	120.5	mL
			TWO	X	1	teaspoonful	(5 gm)						
			One	X	1/4	teaspoonful	(1.1 gm)						
	7	24.8	One	X	1	Tablespoon	(13 gm)	+	109	mL	=	124	mL
			TWO	X	1	teaspoonful	(5 gm)						
			One	X	1/2	teaspoonful	(1.8 gm)						
4	1	26	TWO	X	1	Tablespoon	(13 gm)	+	115	mL	=	130	mL
	2	27.1	TWO	X	1	Tablespoon	(13 gm)	+	120	mL	=	135.5	mL

Table S7A. Open-Label Exposure to Chronic Glycine - Subject 3363: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID)				Glycine	+	Water Amt to Add/ Dose (mL)		=	Glycine 20% Soln Final Volume/Dose (mL)	
			# of Spoonfuls	X	Measuring Spoon Size		(Gm per Spoonful)						
			One	X	1/4	teaspoonful	(1.1 gm)						
	3	28.2	TWO	X	1	Tablespoon	(13 gm)	+	124	mL	=	141	mL
			TWO	X	1/4	teaspoonful	(1.1 gm)						
Week 4, Day 4 & Daily thereafter		28.8	TWO	X	1	Tablespoon	(13 gm)	+	127	mL	=	144	mL
			TWO	X	1/4	teaspoonful	(1.1 gm)						
			One	X	1/8	teaspoonful	(0.6 gm)						

Table S7A. Open-Label Exposure to Chronic Glycine - Subject 3363: Planned Titration

Investigator's Copy: Information for calculating amounts of glycine powder and distilled water

Measuring Spoon Capacity Chart		
Measuring Spoons & Sizes For measuring doses of Glycine powder, according to weight based titration schedule		**Spoon Capacity**[1] In grams of Glycine powder (for lightly measured, level spoonfuls)
Measuring Spoon Set (Endurance®18/10, Stainless Steel) 	**1/8 tea**spoon	0.6 gm
	1/4 teaspoon	1.1 gm
	1/2 teaspoon	1.8 gm
	3/4 teaspoon	3 gm
	1 teaspoon	5 gm
	1 Tablespoon	13 gm
Coffee Scoop- Stainless Steel (Norpro®5537)	**2 Table**spoons	30.4 gm

[1] Measuring Spoon capacities are specific for Glycine powder USP, mfg by Letco Medical, NDC# 62991-2730-03, when measured as directed

Displacement Volume of Glycine Powder in Solution = 0.59 mL/Gm glycine powder
(Specific to Glycine Powder, USP, NDC# 62991-2730-03, Manufactured by Letco Medical)

Glycine & Water Calculations

1. Assign glycine doses for each day of the titration schedule
   Glycine doses for the titration schedule were chosen based on determining reasonable dose increases that could be achieved with the various capacities of the measuring spoons
2. Calculate the total volume that would create a final glycine solution of 20%
   Final Volume (mL) per dose of Glycine 20% Soln = # gm Glycine per dose ÷ 0.2
3. Calculate the amount of water that must be added to each dose of glycine powder to produce the correct final volume as calculated in # 2 above.

Amt of Water (mL) per dose = Final Volume of Glycine 20% Soln (mL) - (# Gm Glycine/dose)(0.59 gm/mL*)

**0.59 gm/mL is the displacement volume of Glycine powder in solution*

Table S8A. Open-Label Exposure to Chronic Glycine - Subject 5459: Planned Titration

Investigator's Copy: Maintenance dose for Subject #5459 of 26 gm/dose (78 gm/day) based on body wt. of 212 lbs (96.4 kg).

Important Note:

- Glycine powder & distilled water are to be measured & mixed, making doses of Glycine 20% solution, which will be taken 3 times/day
- The ***Glycine powder*** must be ***loosened in its jar before*** it is measured (see instructions below)
- ***Glycine powder must be measured lightly with the measuring spoons provided. Do not pack the powder into the measuring spoons***
- The amount of Glycine powder/measuring spoon is specific for spoons filled lightly with loosened Glycine powder ***(not packed)***
- Measure distilled water with the graduated cylinder provided
- Do not mix Glycine solutions ahead of time. Prepare each dose at the time of use
- The total daily dose of Glycine will be increased by approx 4 gm/day (**1.3 gm/dose**) to a maintenance dose of **0.8 gm glycine/kg** body wt

Instructions- Preparing Doses of Glycine 20% Solution

1. Check that the lid is secured on the jar of Glycine powder. Gently roll/rotate jar several times *to loosen the powder before measuring*
2. Refer to the titration schedule for HOW MANY & WHICH SIZE measuring spoons are needed to measure each dose of Glycine powder
3. Lightly fill the first measuring spoon with the Glycine powder (*do not pack powder into the spoon)*
4. Level the measuring spoon with a straight edge *over the jar*, so the excess powder falls back into the jar
5. Transfer the Glycine powder from the measuring spoon into the bottle provided
6. Measure additional spoonful(s) of Glycine Powder (per titration) until the full dose has been measured & placed in the bottle provided
7. Measure the amount of distilled water needed per dose using the graduated cylinder provided (see titration for amount of water/dose)
8. Pour the measured amount of water into the bottle containing the measured dose of Glycine powder
9. Cap bottle & shake for several minutes to dissolve to produce a 20% Glycine solution in the amount needed for the dose
10. Flavor solution to taste using the TrueCitrus® Lemon and Lime flavoring packets provided- Cap bottle & shake to dissolve
    (Note: For the plain TrueLemon and TrueLime flavors, 1 packet = 0.8 gm, which is approximately 1/4 teaspoonful)
11. Drink the entire dose slowly, over a 15 minute period

Table S8A. Open-Label Exposure to Chronic Glycine - Subject 5459: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID)				Glycine	+	Water Amt to Add/ Dose (mL)		=	Glycine 20% Soln Final Volume/Dose (mL)	
			# of Spoonfuls	X	Measuring Spoon Size		(Gm per Spoonful)						
1	1	1.8	One	X	1/2	teaspoonful	(1.8 gm)	+	8	mL	=	9	mL
	2	3	One	X	3/4	teaspoonful	(3 gm)	+	13	mL	=	15	mL
	3	5	One	X	1	teaspoonful	(5 gm)	+	22	mL	=	25	mL
	4	6.1	One	X	1	teaspoonful	(5 gm)	+	27	mL	=	30.5	mL
			One	X	1/4	teaspoonful	(1.1 gm)						
	5	6.8	One	X	1	teaspoonful	(5 gm)	+	30	mL	=	34	mL
			One	X	1/2	teaspoonful	(1.8 gm)						
	6	8	One	X	1	teaspoonful	(5 gm)	+	35	mL	=	40	mL
			One	X	3/4	teaspoonful	(3 gm)						
	7	10	TWO	X	1	teaspoonful	(5 gm)	+	44	mL	=	50	mL
2	1	11.1	TWO	X	1	teaspoonful	(5 gm)	+	49	mL	=	55.5	mL
			One	X	1/4	teaspoonful	(1.1 gm)						
	2	11.8	TWO	X	1	teaspoonful	(5 gm)	+	52	mL	=	59	mL
			One	X	1/2	teaspoonful	(1.8 gm)						
	3	13	One	X	1	Tablespoon	(13 gm)	+	57	mL	=	65	mL
	4	14.1	One	X	1	Tablespoon	(13 gm)	+	62	mL	=	70.5	mL
			One	X	1/4	teaspoonful	(1.1 gm)						
	5	15.4	One	X	1	Tablespoon	(13 gm)						
			One	X	1/2	teaspoonful	(1.8 gm)	+	68	mL	=	77	mL
			One	X	1/8	teaspoonful	(0.6 gm)						
	6	16	One	X	1	Tablespoon	(13 gm)	+	71	mL	=	80	mL
			One	X	3/4	teaspoonful	(3 gm)						
	7	18	One	X	1	Tablespoon	(13 gm)	+	79	mL	=	90	mL
			One	X	1	teaspoonful	(5 gm)						

Table S8A. Open-Label Exposure to Chronic Glycine - Subject 5459: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID)				Glycine	+	Water Amt to Add/ Dose (mL)		=	Glycine 20% Soln Final Volume/Dose (mL)	
			# of Spoonfuls	X	Measuring Spoon Size		(Gm per Spoonful)						
3	1	19.1	One	X	1	Tablespoon	(13 gm)						
			One	X	1	teaspoonful	(5 gm)	+	84	mL	=	95.5	mL
			One	X	1/4	teaspoonful	(1.1 gm)						
	2	19.8	One	X	1	Tablespoon	(13 gm)						
			One	X	1	teaspoonful	(5 gm)	+	87	mL	=	99	mL
			One	X	1/2	teaspoonful	(1.8 gm)						
	3	21	One	X	1	Tablespoon	(13 gm)						
			One	X	1	teaspoonful	(5 gm)	+	93	mL	=	105	mL
			One	X	3/4	teaspoonful	(3 gm)						
	4	21.6	One	X	1	Tablespoon	(13 gm)						
			One	X	1	teaspoonful	(5 gm)						
			One	X	3/4	teaspoonful	(3 gm)	+	95	mL	=	108	mL
			One	X	1/8	teaspoonful	(0.6 gm)						
	5	23.6	One	X	1	Tablespoon	(13 gm)						
			TWO	X	1	teaspoonful	(5 gm)	+	104	mL	=	118	mL
			One	X	1/8	teaspoonful	(0.6 gm)						
	6	24.1	One	X	1	Tablespoon	(13 gm)						
			TWO	X	1	teaspoonful	(5 gm)	+	106	mL	=	120.5	mL
			One	X	1/4	teaspoonful	(1.1 gm)						
	7	24.8	One	X	1	Tablespoon	(13 gm)						
			TWO	X	1	teaspoonful	(5 gm)	+	109	mL	=	124	mL
			One	X	1/2	teaspoonful	(1.8 gm)						
4	1	26	TWO	X	1	Tablespoon	(13 gm)	+	115	mL	=	130	mL
	2	27.1	TWO	X	1	Tablespoon	(13 gm)	+	119.5	mL	=	135.5	mL

Table S8A. Open-Label Exposure to Chronic Glycine - Subject 5459: Planned Titration

Week #	Day #	Glycine Gm Per Dose (3 X/day)	Glycine Powder- Amount/Dose (TID)				Glycine	+	Water Amt to Add/ Dose (mL)		=	Glycine 20% Soln Final Volume/Dose (mL)	
			# of Spoonfuls	X	Measuring Spoon Size		(Gm per Spoonful)						
			One	X	1/4	teaspoonful	(1.1 gm)						
	3	28.2	TWO	X	1	Tablespoon	(13 gm)	+	124.4	mL	=	141	mL
			TWO	X	1/4	teaspoonful	(1.1 gm)						
Week 4, Day 1 & Daily thereafter		26	TWO	X	1	Tablespoon	(13 gm)	+	115	mL	=	130	mL

Table S8A. Open-Label Exposure to Chronic Glycine - Subject 5459: Planned Titration

Investigator's Copy: Information for calculating amounts of glycine powder and distilled water

Measuring Spoon Capacity Chart		
Measuring Spoons & Sizes For measuring doses of Glycine powder, according to weight based titration schedule		**Spoon Capacity**[1] In grams of Glycine powder (for lightly measured, level spoonfuls)
Measuring Spoon Set (Endurance®18/10, Stainless Steel) 	**1/8 tea**spoon	0.6 gm
	1/4 teaspoon	1.1 gm
	1/2 teaspoon	1.8 gm
	3/4 teaspoon	3 gm
	1 teaspoon	5 gm
	1 Tablespoon	13 gm
Coffee Scoop- Stainless Steel (Norpro®5537)	**2 Table**spoons	30.4 gm

[1] Measuring Spoon capacities are specific for Glycine powder USP, mfg by Letco Medical, NDC# 62991-2730-03, when measured as directed

Displacement Volume of Glycine Powder in Solution = 0.59 mL/Gm glycine powder
(Specific to Glycine Powder, USP, NDC# 62991-2730-03, Manufactured by Letco Medical)

Glycine & Water Calculations

1. Assign glycine doses for each day of the titration schedule
   Glycine doses for the titration schedule were chosen based on determining reasonable dose increases that could be achieved with the various capacities of the measuring spoons
2. Calculate the total volume that would create a final glycine solution of 20%
   Final Volume (mL) per dose of Glycine 20% Soln = # gm Glycine per dose ÷ 0.2
3. Calculate the amount of water that must be added to each dose of glycine powder to produce the correct final volume as calculated in # 2 above.

Amt of Water (mL) per dose = Final Volume of Glycine 20% Soln (mL) - (# Gm Glycine/dose)(0.59 gm/mL*)

**0.59 gm/mL is the displacement volume of Glycine powder in solution*

Figure S1: Comparative Genome Hybridization Array (aCGH) Analysis showing the presence of the duplicated and triplicated regions in the two carriers but not in the proband's siblings, father or maternal grandparents. Absence of the copy number variant (CNV) in the mother's siblings was verified but is not shown. Courtesy of J Sebat, S McCarthy, and D Malhotra.

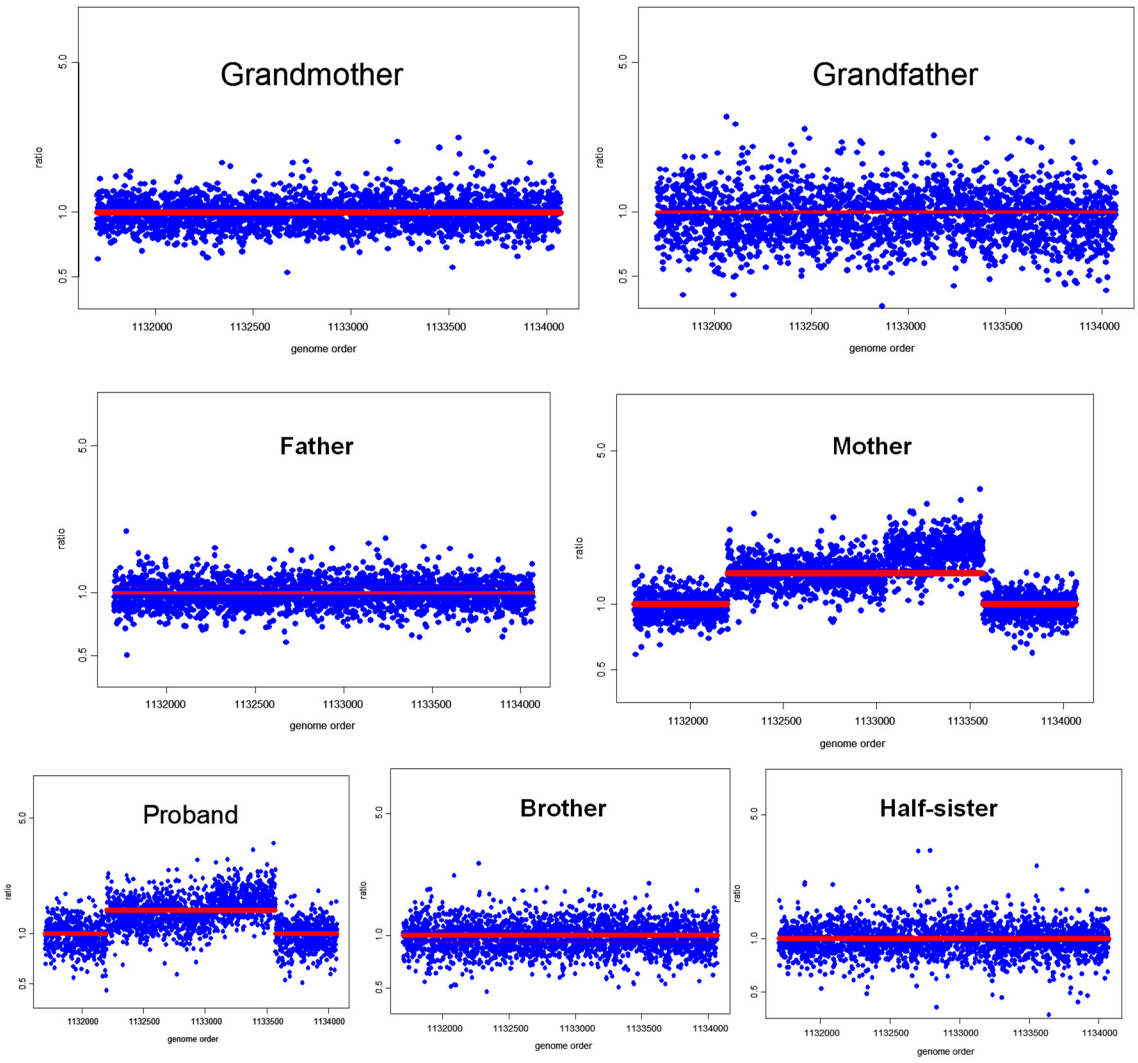


Figure S2. Changes in Positive and Negative Syndrome Scale (PANSS) Domains as a Function of Treatment with Glycine or Placebo. Domains salient for subject 5459: conceptual disorganization (A), impulse control (B), positive symptoms (C). Changes in PANSS domains salient for subject 3363: delusions (D), blunted affect (E), positive symptoms (F), and negative symptoms (G). All data are from the acute trials.

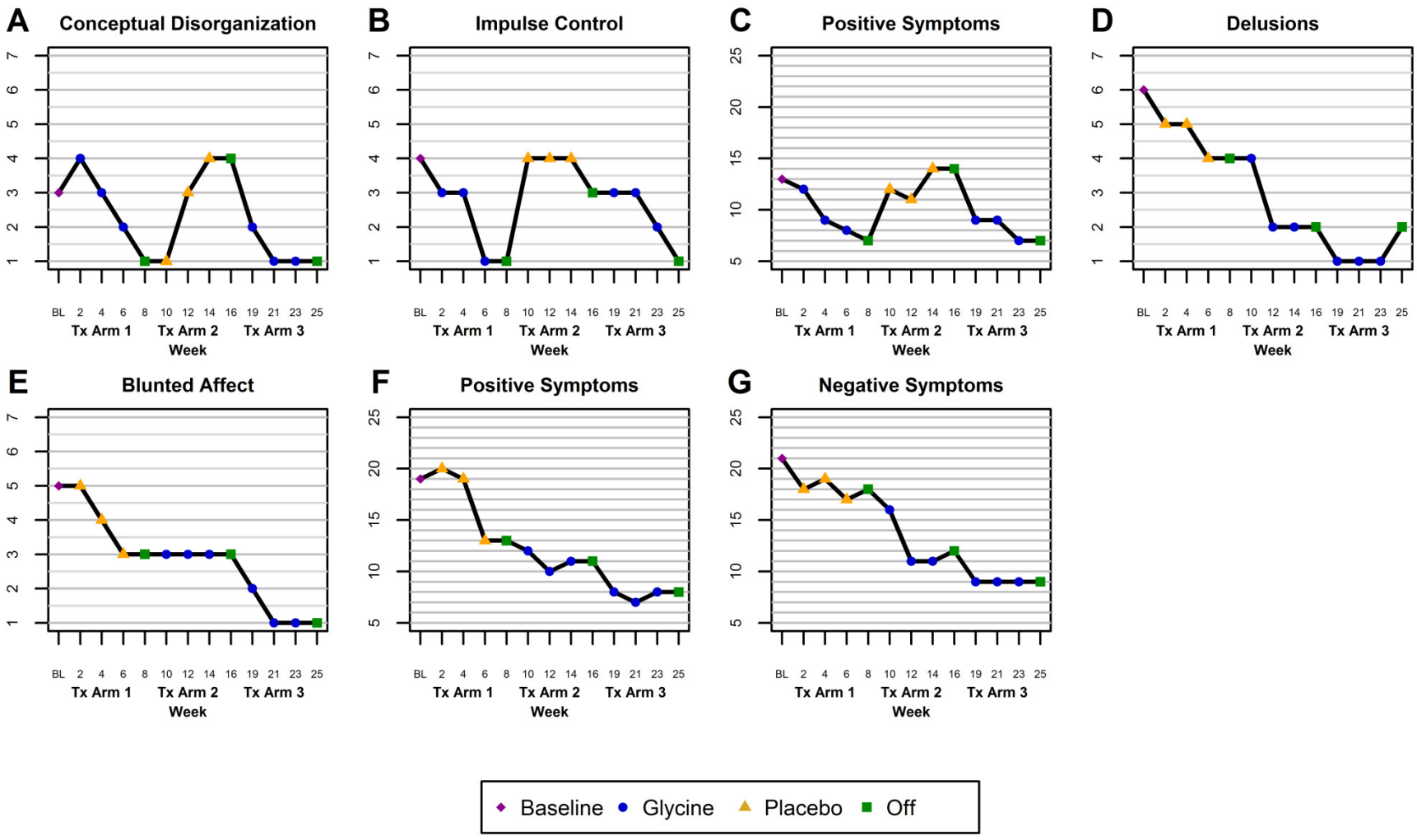


Figure S3: Changes in Mania and Depressive Symptoms as a Function of Treatment with Glycine or Placebo in Subject 5459**.** (A) Changes in mania symptoms (Young Mania Rating Scale). (B) Changes in depressive symptoms (Hamilton Depression Scale).

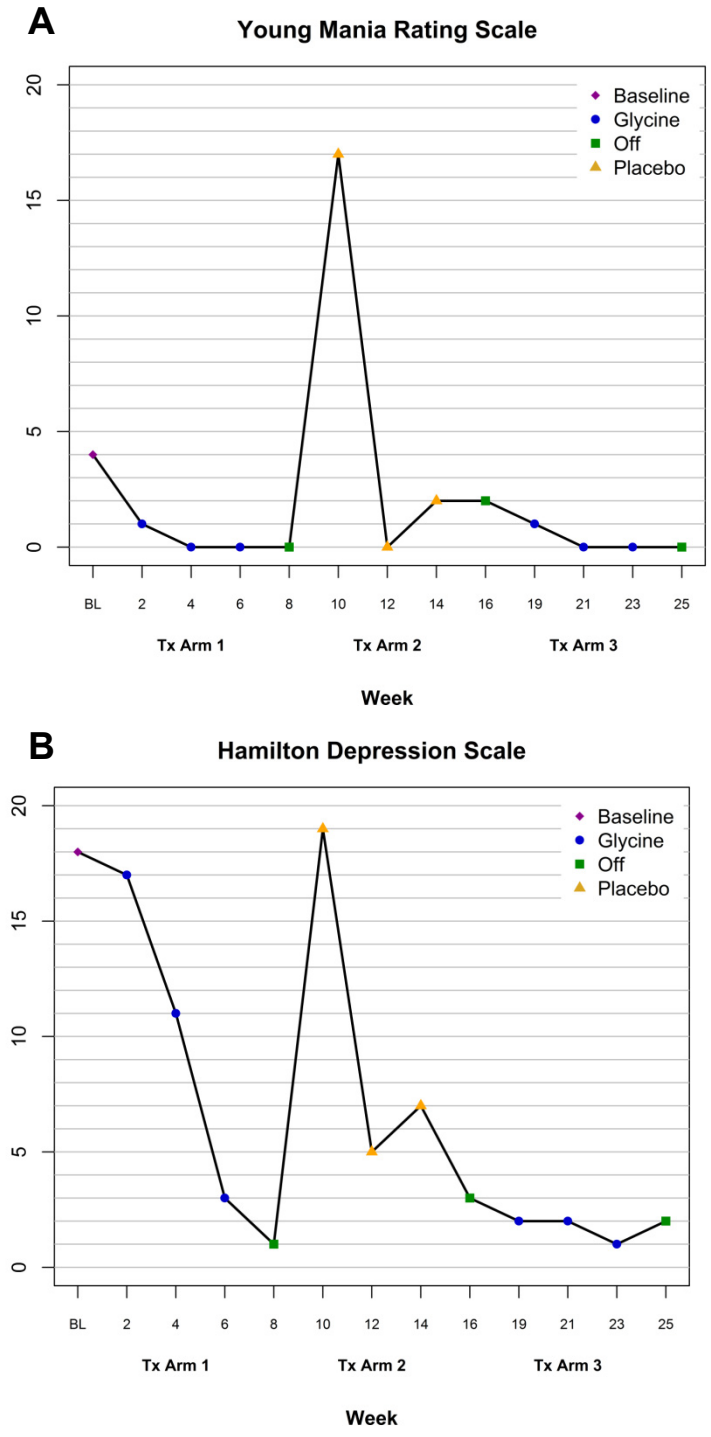


Figure S4: Changes in Plasma Kynurenine (KYN) Level as a Function of Treatment with Glycine or Placebo or DCS or Placebo. (A) Glycine or placebo, subject 5459. (B) Glycine or placebo, subject 3363. (C) DCS or placebo, subject 5459. (D) DCS or placebo, subject 3363.

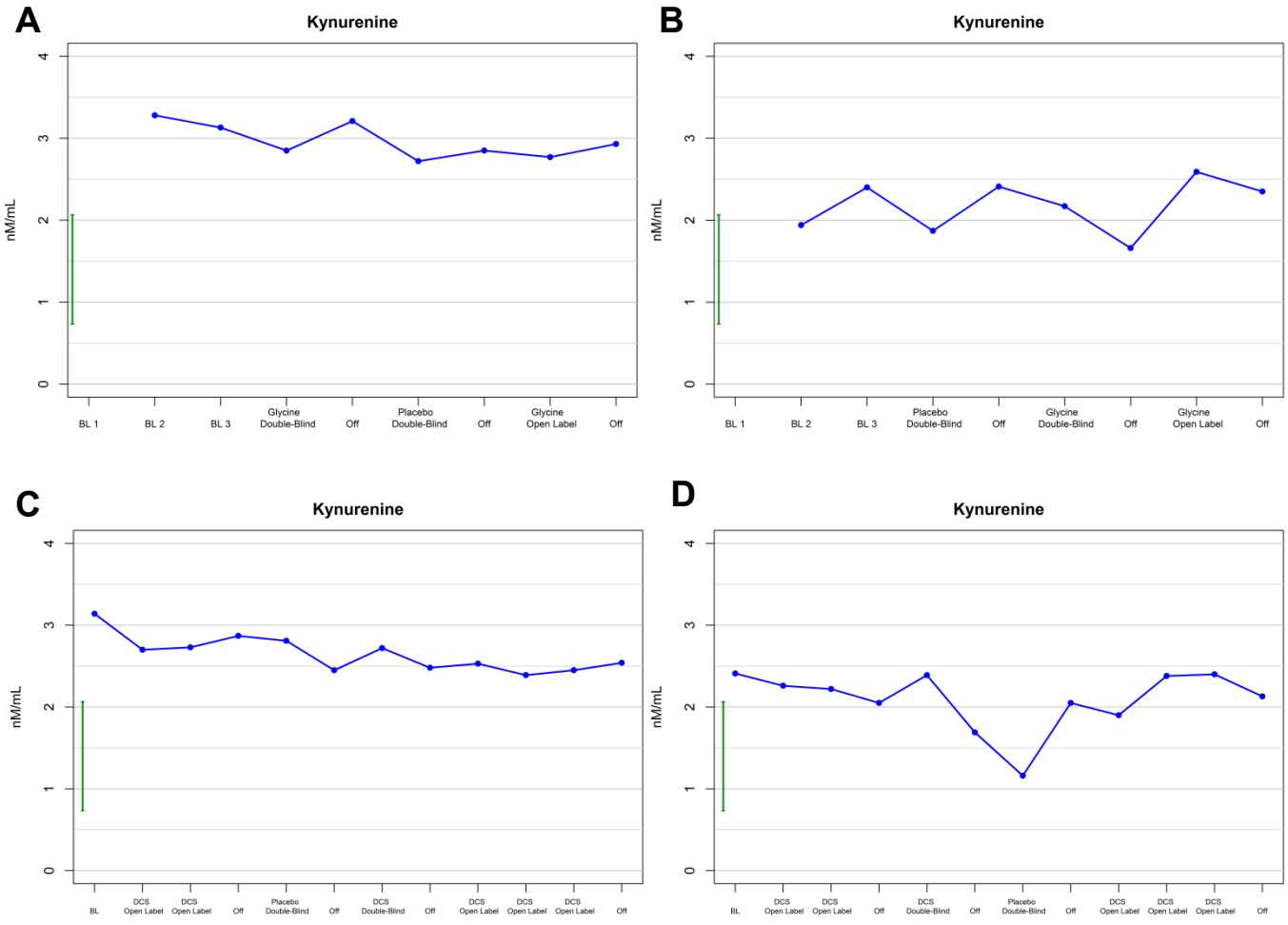


Figure S5: Changes in Plasma Kynurenic Acid (KYNA) Level as a Function of Treatment with Glycine or Placebo or DCS or Placebo. (A) Glycine or placebo, subject 5459. (B) Glycine or placebo, subject 3363. (C) DCS or placebo, subject 5459 (D) DCS or placebo, subject 3363.

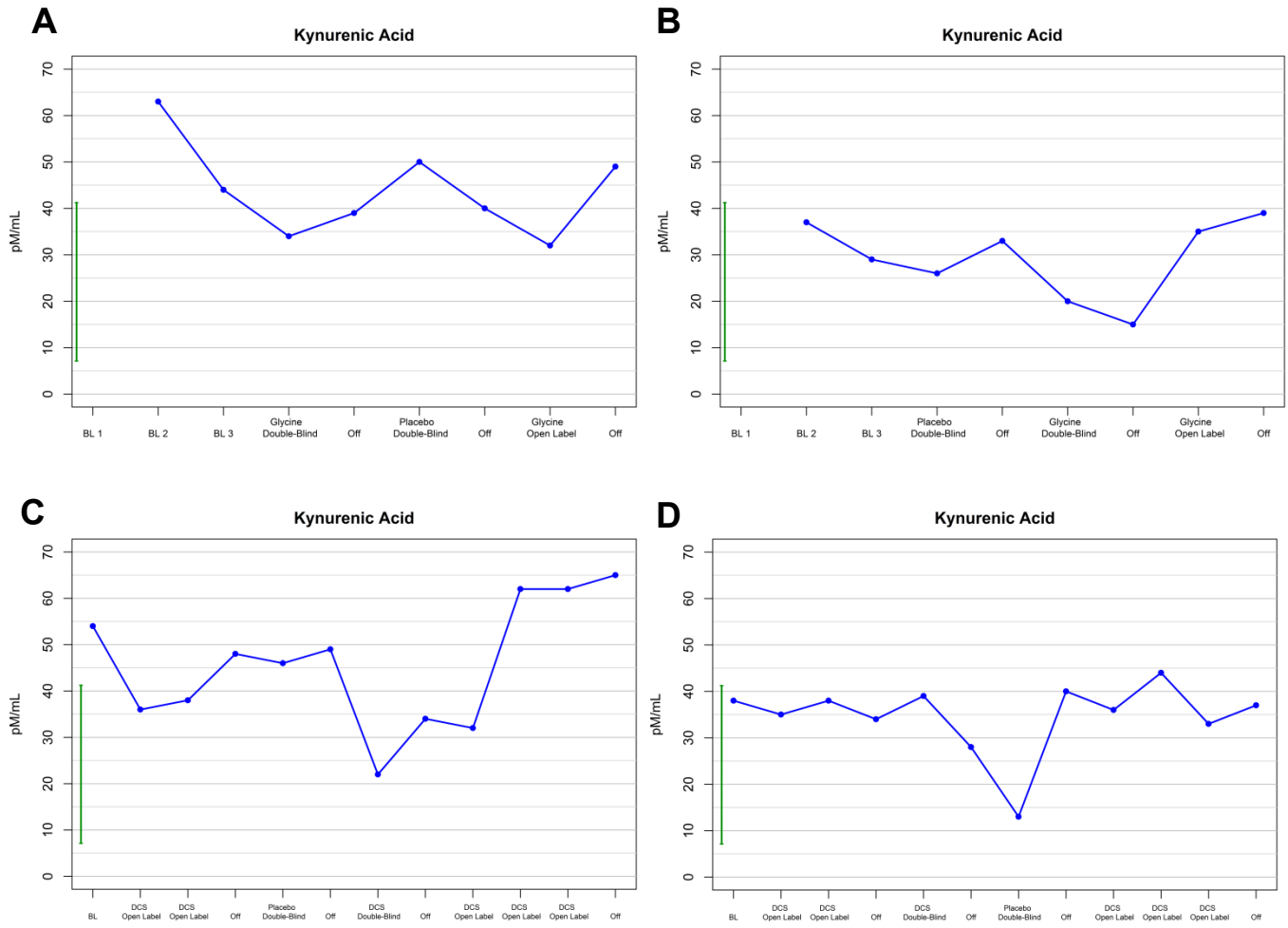


Figure S6: Changes in Plasma Glycine Level as a Function of Treatment with DCS or Placebo. (A) Subject 5459. (B) Subject 3363.

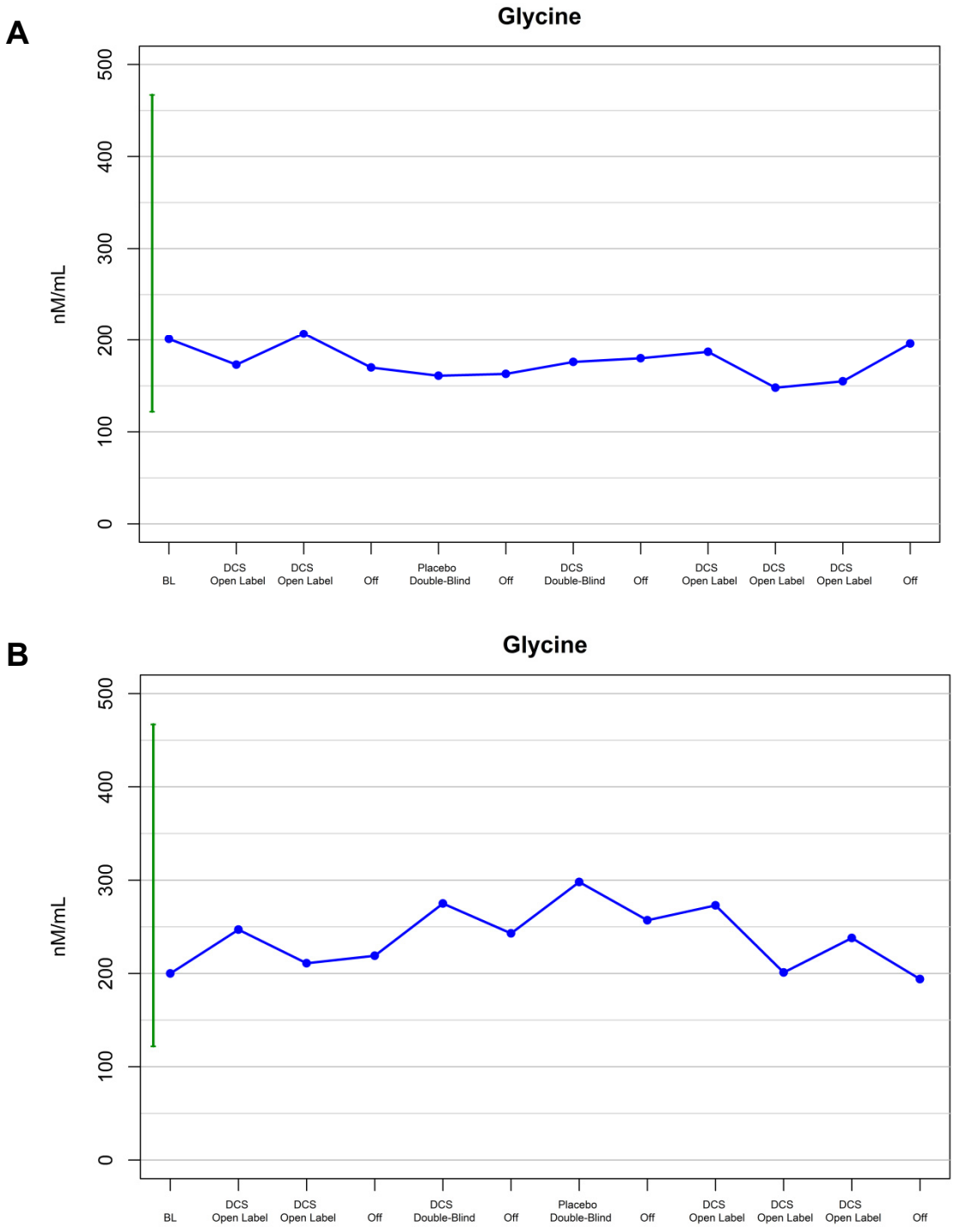


Figure S7: Changes in MATRICS Cognitive Domains and Overall Composite Score as a Function of Glycine, DCS and Placebo**.** (A) Subject 5459. (B) Subject 3363.

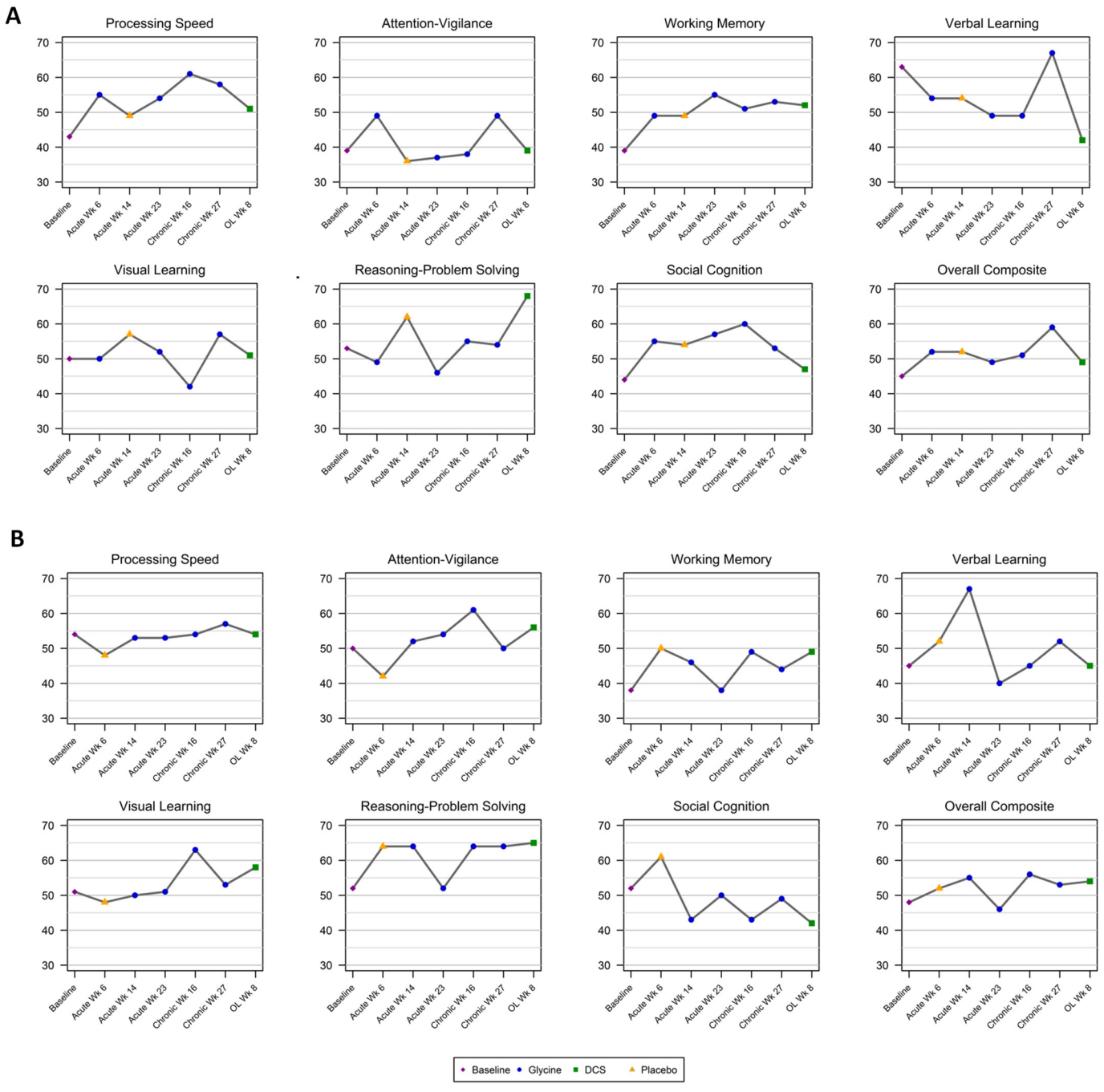


Figure S8. Schematic Illustrating Possible Mechanism of Action of Glycine and DCS Augmentation. Glutamate signaling through NMDA receptors requires glycine or D-serine at the glycine modulatory site (GMS). Kynurenic acid (KYNA) competitively blocks the GMS, while excess glycine decarboxylase (GLDC) depletes both glycine and d-serine. D-cycloserine can out-compete KYNA to restore NMDA receptor function and augment treatment [Modified from (68)].

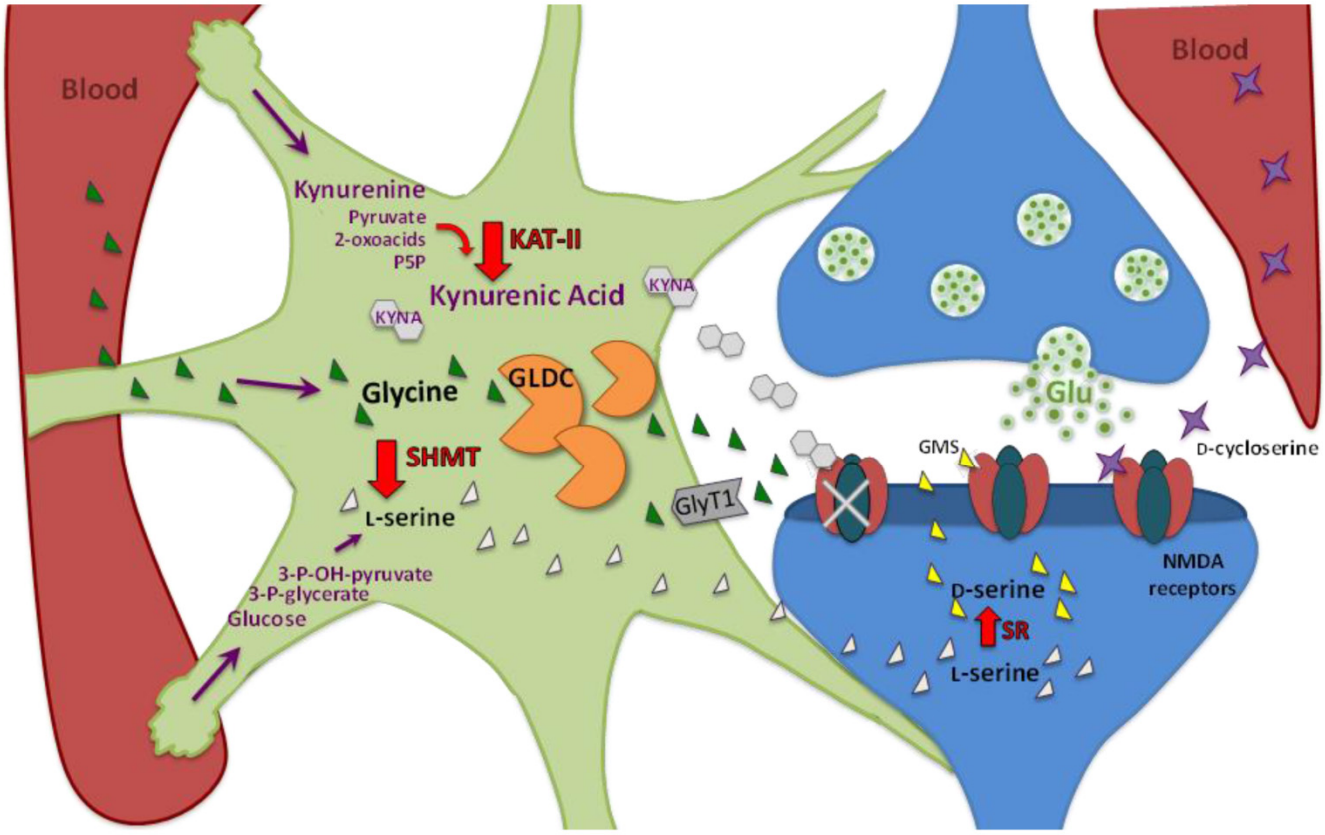
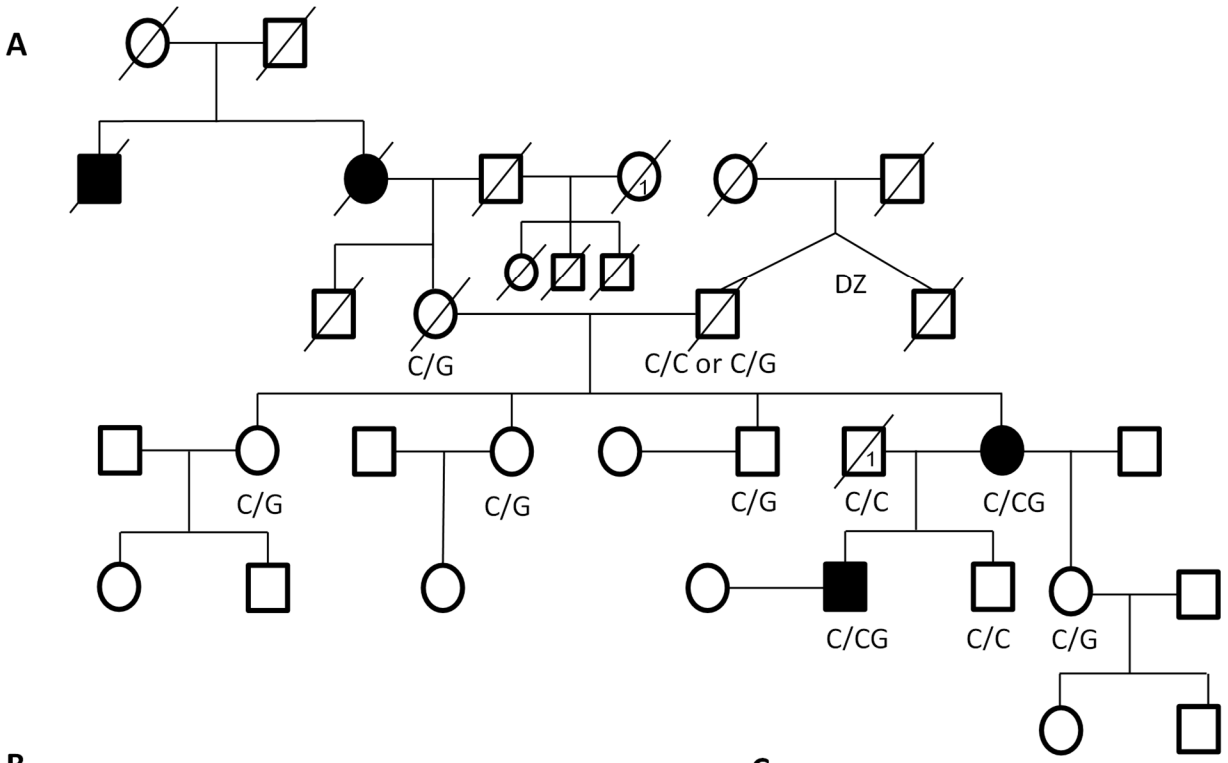


Figure S9: GLDC SNP Dosage. Genotypes of SNP rs10975641 of the *GLDC* Gene. (A) Based on family structure, only the G allele could carry the CNV. Individual genotypes noted in figure. Proband's maternal grandfather not genotyped due to lack of biological material. Twenty unrelated individuals were also genotyped. (B) Consistent with the triplication of *GLDC*, quantitative PCR SNP genotyping showed that carriers had equal proportions of each SNP allele, consistent with a genotype of C/CGG, as would be predicted by the triplication. Although the carriers are heterozygous for the SNP, their dosage levels (delta delta CT values) did not differ from those of non-carrier homozygotes for both the C and G allele (Ps>0.2). Delta delta CT values of the carriers were significantly lower than those of non-carrier heterozygotes for both the C allele ($P = 2.6^{-13}$) and the G allele ($P = 8.2^{-9}$). Lower delta-delta CTs correspond to higher allele dosages. The two copy heterozygotes have higher delta-delta CTs, because they have only one of each allele compared with the two copy homozygotes and four copy carriers. In contrast, the carriers and homozygotes are comparable. Courtesy of Scott Hebbring.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DZ
C/G
C/C or C/G
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C/G
C/G
C/C
C/CG
C/CG
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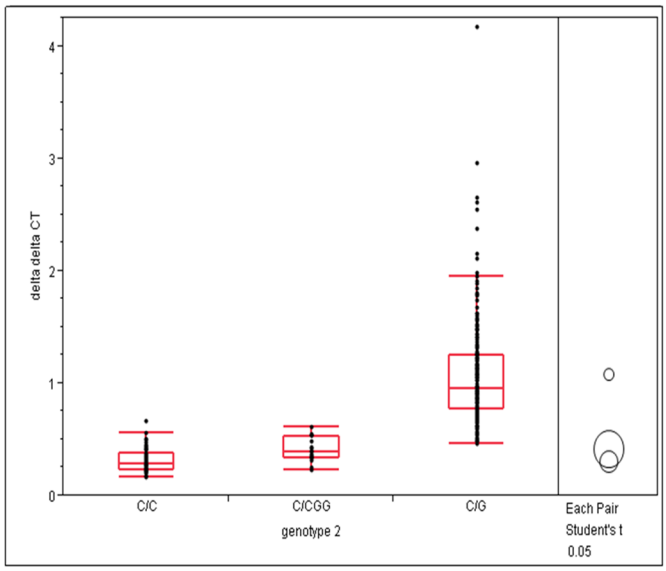
C/G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delta delta CT
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C/G
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Each Pair
Student's t
0.05

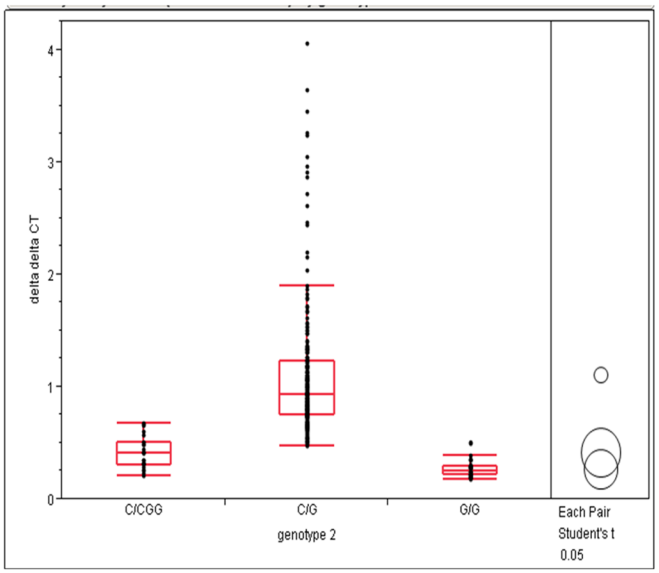
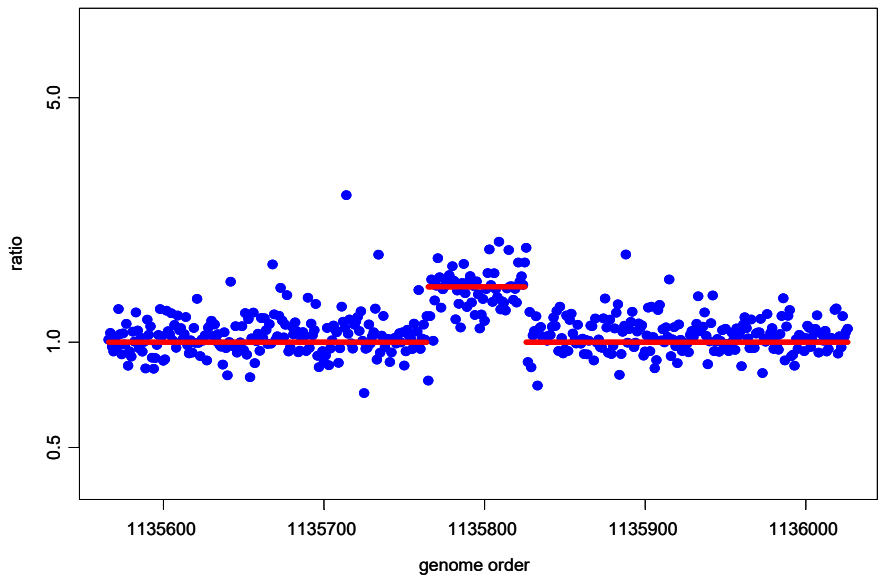

C
delta delta CT
C/CGG
C/G
G/G
genotype 2
Each Pair
Student's t
0.05

Figure S10: Intronic Duplication in *PTPRD*. Courtesy of J Sebat, S McCarthy, and D Malhotra.



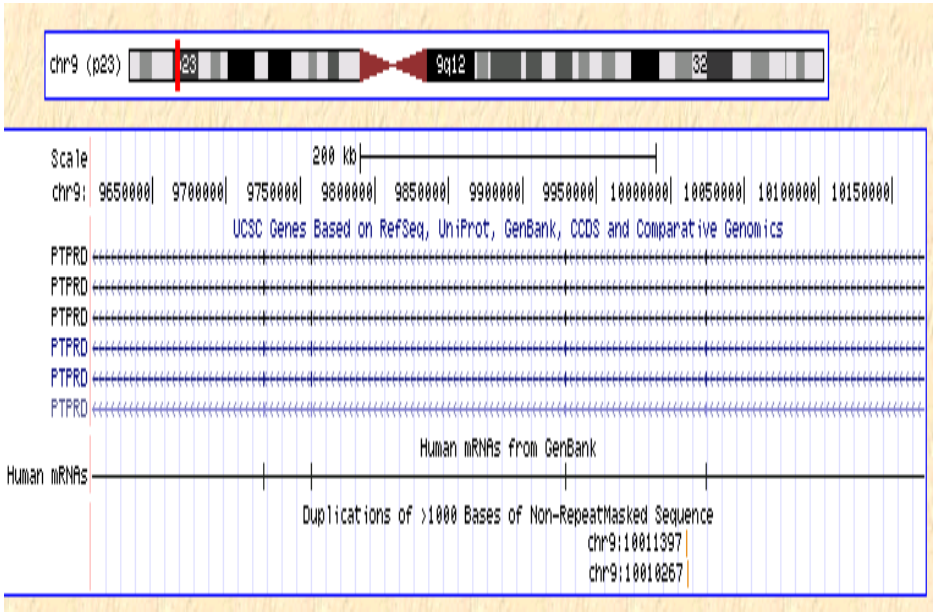


Figure S11: Changes in Severity of Illness (Clinical Global Impression Scale, CGI) as a Function of Treatment with Glycine or Placebo**.** (A) Subject 5459. (B) Subject 3363. 4: Moderately ill; 3 Mildly ill; 2: Borderline ill.

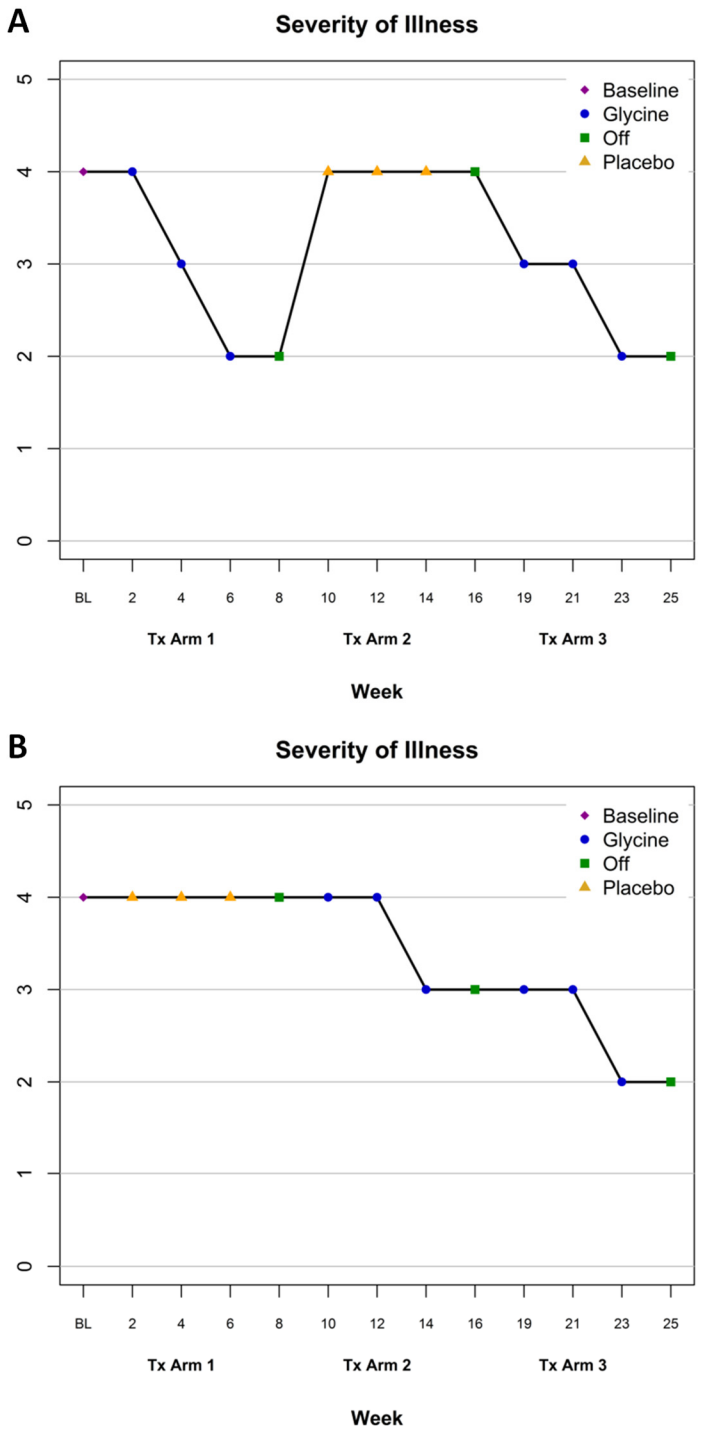


Figure S12. Glycine/Placebo Supplies. Labeling on (A) front and (B) back of glycine/placebo bottles during the acute glycine augmentation trial. (C) Packaging of daily/weekly doses. (D) Blind envelope. (E) Used dosage bottles returned to pharmacy for disposal. (F) Glycine and supplies used in the chronic glycine treatment arm.

Figure S13. Changes in Positive and Negative Syndrome Scale (PANSS) Domains as a Function of Treatment with DCS or Placebo. Domains salient for Subject 5459: conceptual disorganization (A), impulse control (B), positive symptoms (C). Changes in PANSS Domains Salient for Subject 3363: delusions (D), blunted affect (E), positive symptoms (F), and negative symptoms (G). All data are from the acute trials.

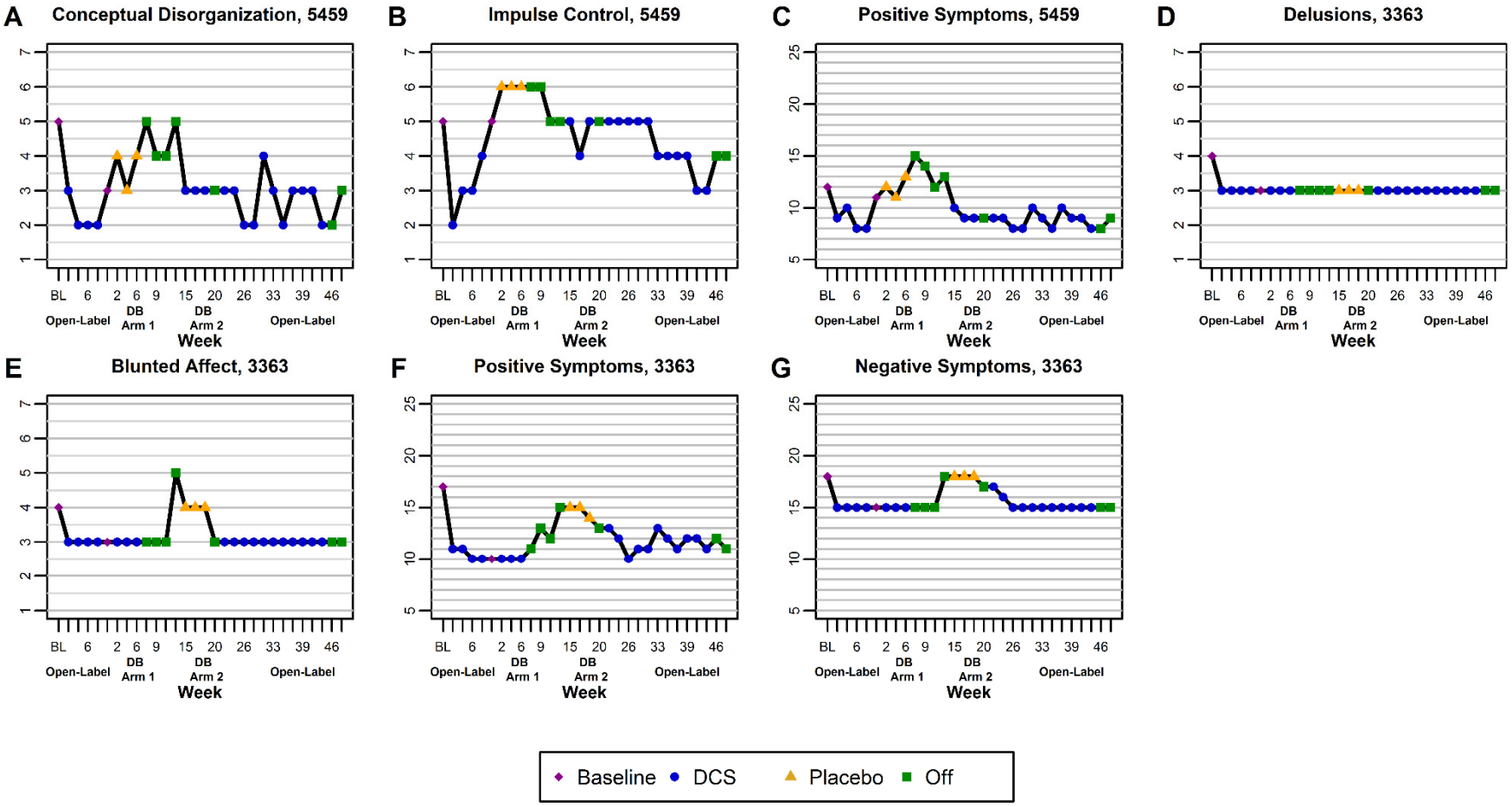
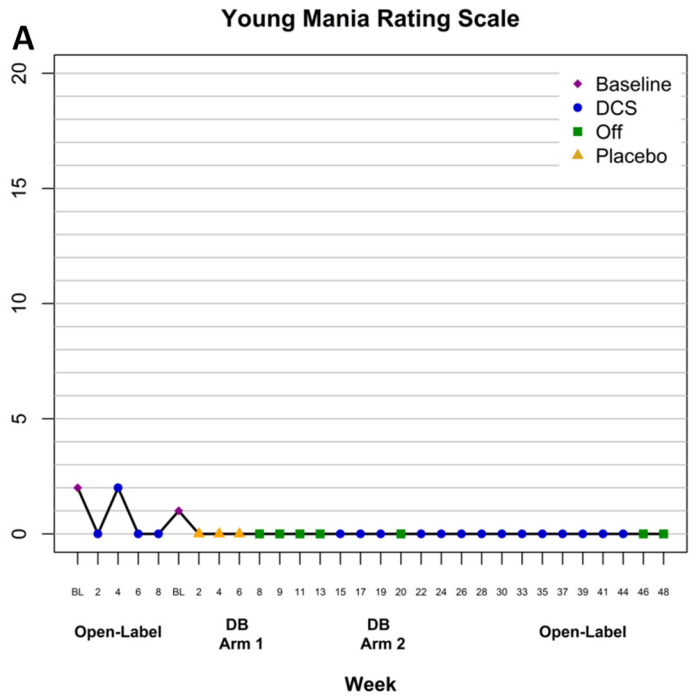


Figure S14: Changes in Mania and Depressive Symptoms as a Function of Treatment with DCS or Placebo in Subject 5459. (A) Changes in mania symptoms (Young Mania Rating Scale). (B) Changes in depressive symptoms (Hamilton Depression Scale).



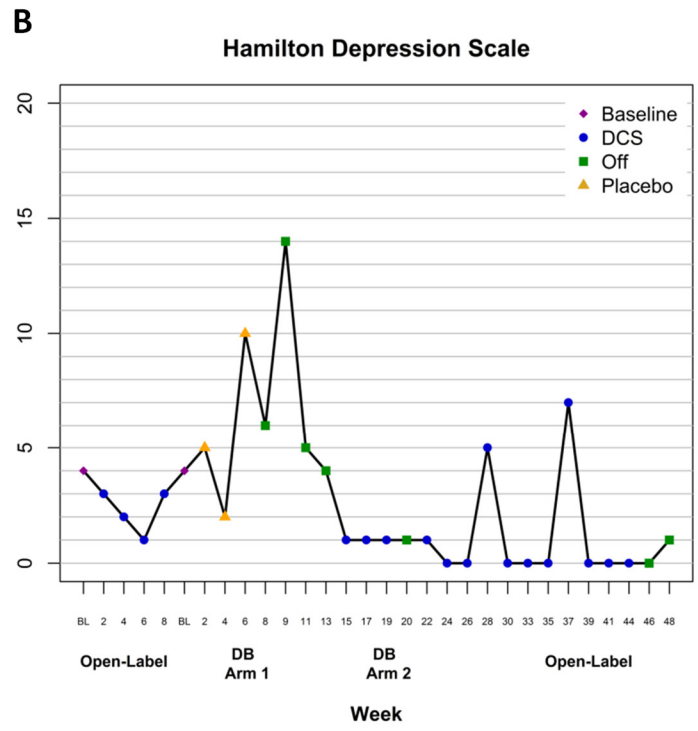


Figure S15: Changes in Severity of Illness (CGI) as a Function of Treatment with DCS or Placebo. (A) Subject 5459. (B) Subject 3363. 4: Moderately ill; 3 Mildly ill; 2: Borderline ill.

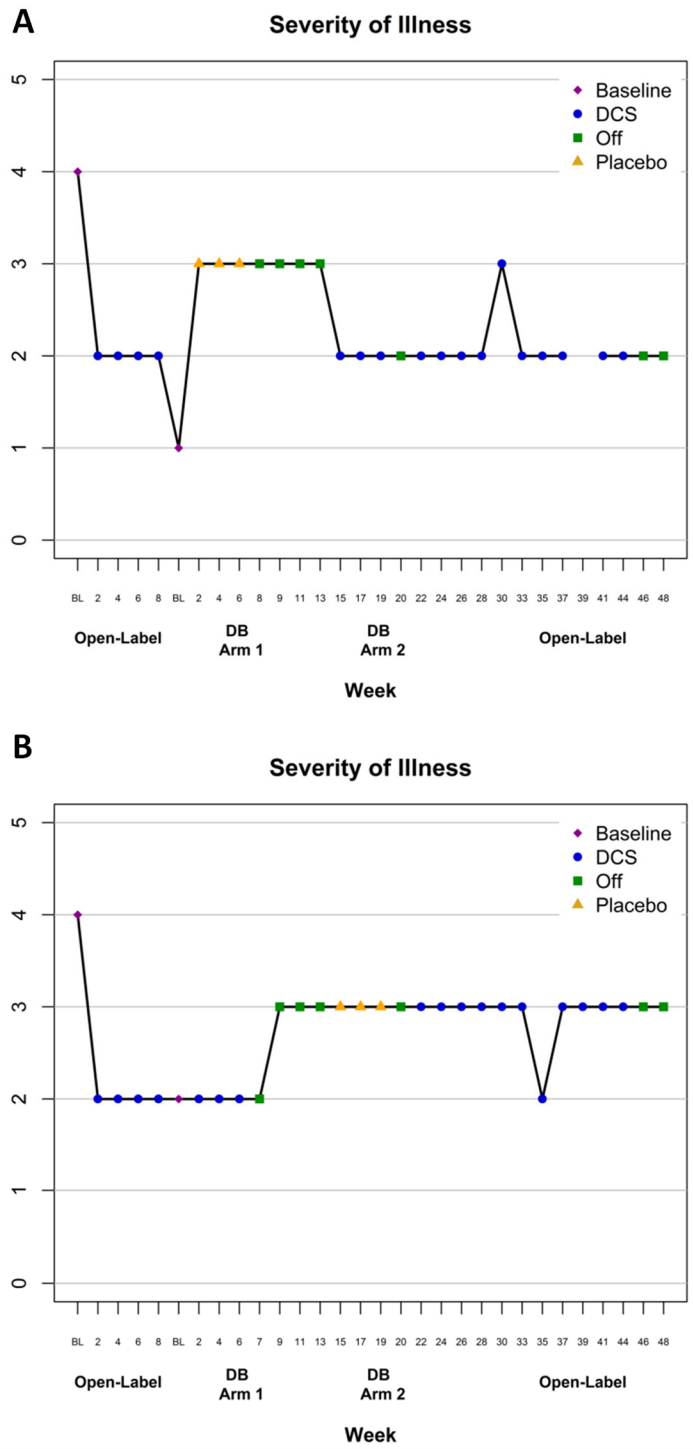


Figure S16: Sequencing of a Schizophrenia Patient from the Rujescu Cohort (47) by the Lupski Lab, Baylor College of Medicine. *GLDC* is completely deleted and *KDM4C* is partially deleted. *IL33*, *TD52L3*, and *UHRF2* are also deleted.

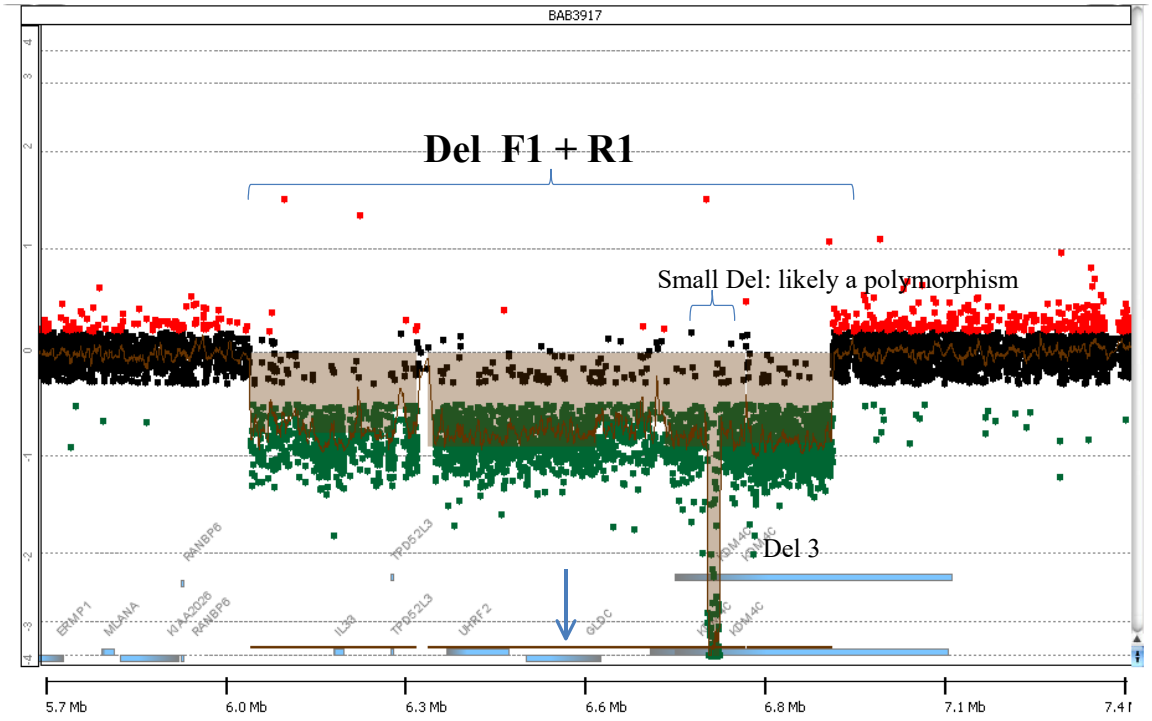
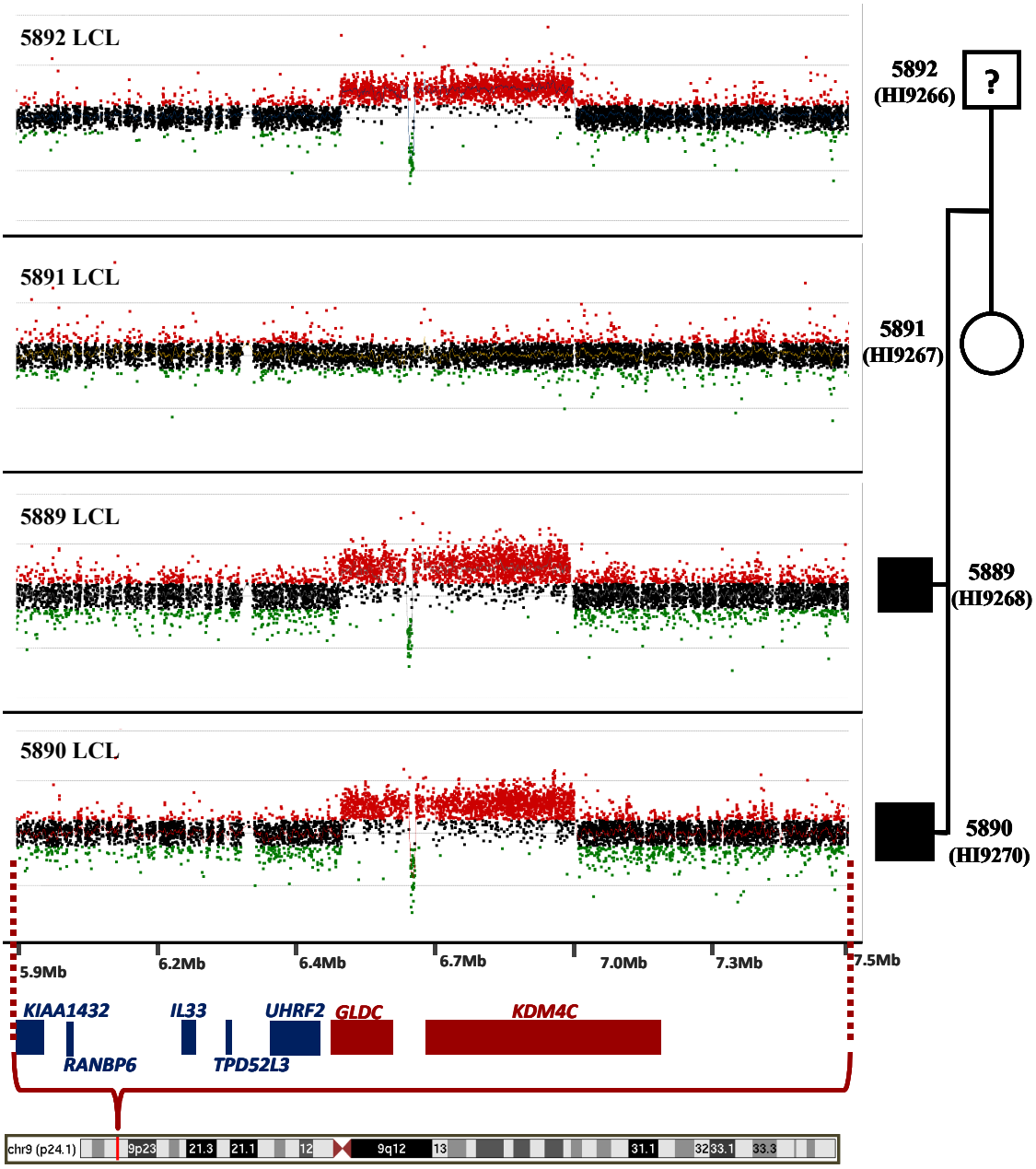


Figure S17: Sequencing of Autism Genetic Research Exchange Family AU2372 (61) by the Lupski Lab, Baylor College of Medicine. Two ASD/PPD brothers, one with autism spectrum disorder, one with pervasive developmental disorder, had a paternally inherited partial duplication of *GLDC/KDM4C.*

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