January 2012

Anticholinergic Impact On Cognition In Schizophrenia

Catherine Underwood
Yale University, cat.underwood@gmail.com

ANTICHOLINERGIC IMPACT ON COGNITION IN SCHIZOPHRENIA

Original Thesis
Submitted to the Faculty
Yale University School of Nursing

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Nursing

Catherine Lindsey Underwood

May 21, 2012

This thesis is accepted in partial fulfillment of the requirements for the degree Master of Science in Nursing.

Advisor: Lawrence Scahill, MSN, PhD

Date: 16 May 2012

Permission for printing, photocopying or microfilming of "Anticholinergic Impact on Cognition in Schizophrenia" for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law of unpublished manuscripts.

_____

Acknowledgments

The research for the primary study from which this data was received was made possible by the grant of Dr. Morris Bell, PhD. Members of the primary study who assisted in the inspiration and execution of this secondary analysis as well as in editing the manuscript include Drs. Toral Surti, MD, PhD, Silvia Corbera, PhD, and Cenk Tek, MD. Advisor for the paper was Dr. Lawrence Scahill, MSN, PhD.

ABSTRACT

ANTICHOLINERGIC IMPACT ON COGNITION IN SCHIZOPHRENIA

This secondary analysis examined the relationship between the total anticholinergic load and scores on cognitive tests in 94 patients diagnosed with schizophrenia or schizoaffective disorder. Cognitive impairment is a core feature of schizophrenia, and studies have shown that it is a strong predictor of functional outcomes in this population. Anticholinergic medications have been demonstrated to have a negative impact on cognition. Some antipsychotic medications have anticholinergic properties, and anticholinergic medications are often prescribed to patients with schizophrenia to treat or prevent extrapyramidal side effects of antipsychotics. We did not find any significant correlations between anticholinergic load as measured by benztropine equivalents and any of the MATRICS cognitive tests. In addition there were no significant differences in the mean scores of subjects in the highest anticholinergic quartile and subjects in the lowest anticholinergic quartile. These same analyses were performed comparing chlorpromazine equivalents and again there were no statistically significant results. Our results suggest that the anticholinergic load or dose of antipsychotic medication do not significantly contribute to cognitive deficits in patients with schizophrenia or schizoaffective disorder. The relatively small sample size was inadequate to detect a small difference.

TABLE OF CONTENTS

TABLES AND FIGURES

Introduction

Schizophrenia is a chronic psychiatric disorder affecting about 1% of the population worldwide. Although it is most often characterized by the positive and negative symptoms, impaired cognition is also a core feature of this disorder (Goldberg & Green, 2002; Velligan & Miller, 1999; Sharma & Antonova, 2003; O'Carroll, 2000. It is likely that these deficits in cognition predate the onset of positive or negative symptomatology (Green, 1996). Patients experiencing their first psychotic episode and patients with chronic schizophrenia perform poorly on tests of memory, executive functioning and attention (Goldberg & Green, 2002). Over the past decade, treatments for schizophrenia are increasingly targeting cognitive impairments (Fumagalli, Frasca, Racagni, & Riva, 2009; Weiss, Bilder, & Fleischhacker, 2002; Velligan & Miller, 2003).

In patients with schizophrenia, cognitive abilities predict and correlate with functional outcome (Green, 1996; Goldberg & Green, 2002; Kurtz, Wexler, Fujimoto, Shagan, & Seltzer, 2008; Weiss et al., 2002), more strongly than psychotic symptoms (Green, 1996). Specifically, secondary verbal memory (delayed recall as opposed to immediate recall) is a strong predictor of functional outcome regardless of which specific functional task is being measured (Green, 1996). Additionally, there is evidence that employment is predicted by speed of processing, (with this predictive power improving with the addition of visual learning and attention/vigilance assessment scores) (Kern et al., 2011) and working memory performance (Shamsi et al., 2011). Skill acquisition is associated with verbal memory and vigilance (Green, 1996) and social functioning is predicted by social cognition and attention (Shamsi et al., 2011) and vigilance (Green, 1996).

It is not uncommon for patients with schizophrenia to be prescribed anticholinergic medications. Anticholinergic medications inhibit acetylcholine activity by occupying its receptors. There is particular interest in the muscarinic subtype of acetylcholine receptors, as it is these receptors, rather than the nicotinic subtype, upon which psychiatric medications demonstrate activity. Scopolamine, an anticholinergic medication, is used in neuropsychopharmacological studies to induce cognitive deficits in humans and animals (Klinkenberg & Blokland, 2010). Acetylcholine receptor antagonists decrease muscle tremors and rigidity and are often used to prevent or treat extrapyramidal symptoms in patients on antipsychotics. Campbell et al. (2009) systematically reviewed 27 studies and found a consistent association between cognitive impairments in older adults and the use of anticholinergic medications. Specifically, exposure to anticholinergic medications was found to correlate with deficits in speed of processing, concentration and attention, problem-solving (Campbell et al., 2009) and verbal memory (Brebion, Bressan, Amador, Malaspina, & Gorman, 2004).

Antipsychotic medications, which are prescribed for the treatment of schizophrenia, may also have anticholinergic properties (Ozbilen & Adams, 2009). In addition, many patients are on more than one antipsychotic at a time (Zink, Englisch, & MeyerLindenberg, 2010). Are we prescribing psychiatric medications that contribute to the cognitive impairment of patients with schizophrenia?

Vinogradov, Fisher, Warm, Holland, Kirshner, and Pollock (2009) examined the relationship between the anticholinergic load of medications taken and the response to cognitive training in 55 patients. The patients were randomly assigned to either auditory cognitive computer training or a computer games control condition. Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)-recommended measures were

administered at baseline and after intervention. Blood samples were obtained at baseline for all participants, and a radioreceptor binding assay was used to determine serum anticholinergic activity. Blood samples taken at 10 weeks from a random sample of participants indicated that serum anticholinergic levels remained constant throughout the study. For all participants at baseline, there was a significant negative correlation between anticholinergic activity as measured by serum levels and verbal working memory ($r = –0.41$, $p<0.04$) and verbal learning and memory ($r = –0.29$, $p<0.04$). In verbal working memory, 56% variance was attributed to anticholinergic activity, age, IQ, and symptom severity with 37% variance attributed to these same factors in verbal learning and memory. In both domains, 7% of the variance was uniquely attributed to anticholinergic load, independent of the other factors. In the intervention group, anticholinergic load was demonstrated to have a significant negative impact on participants' response to cognitive training (Pearson's $r = –0.46$, $p<0.02$). In this group, anticholinergic activity uniquely accounted for 20% of the variance in cognitive change, which is significantly more than age, IQ, or symptom severity accounted for. Additionally, participants with lower anticholinergic activity had greater cognitive gains after cognitive remediation, a treatment aimed to improve cognitive problems.

The present analysis is a post-hoc analysis of a larger on-going study of cognitive remediation's effects on vocational outcomes in schizophrenia and schizoaffective disorder. The purpose of this secondary analysis is to test whether anticholinergic load is associated with lower cognitive performance on tests of verbal learning and working memory.

Methods

Setting and Subjects

This secondary analysis included 94 adult outpatients (male=54, female=40) with schizophrenia (n=65) or schizoaffective disorder (n=27), who participated in a randomized

controlled trial combining computerized-based cognitive remediation with vocational rehabilitation at a community mental health center in Connecticut. Diagnoses were made following a clinical assessment. Inclusion and exclusion criteria for the main study are as follows: diagnosis of schizophrenia or schizoaffective disorder, no history of head trauma, no history of epilepsy, loss of consciousness; developmental delay; mental retardation, clinically stable (no hospitalization or medication change in the past month), no active abuse of substances in the past 60 days, stable housing (no housing changes in the last 30 days), interested in obtaining competitive employment in the community, willing to do cognitive training if randomized to that condition.

The main study has not yet been published, but one post-hoc analysis has been described in Surti, Corbera, Bell, and Wexler (2011). The main study included 98 total patients, but four were left out of our secondary analysis: one patient was simultaneously engaged in a double-blind, placebo-controlled, antipsychotic medication study; and three patients had incomplete medication information.

Procedures

Upon intake and at each follow-up in the main study, participants completed a history form that included a concomitant medication record. These records were verified against participants' ongoing treatment records in 79.8% of cases (n=75). Eighty-eight of 94 participants were on psychiatric medications. Using recorded data, chlorpromazine and benztropine equivalents were calculated for each patient. Chlorpromazine dose equivalency calculations were done using ratios from Andreasen, Pressler, Nopoulos, Miller, and Ho (2010). This method used expert consensus and regression equations to derive formulas for each drug's potency relative to chlorpromazine. The dosage of each antipsychotic medication was multiplied

by its respective ratio to ascertain its equivalence to 100mg of chlorpromazine. If a patient was on multiple antipsychotics, the chlorpromazine equivalences of each medication were added together to derive the patient's total chlorpromazine load. Benztropine equivalents were calculated for all patients on psychiatric medications (antipsychotics, antidepressants and anticholinergics) known to have anticholinergic activity. Benztropine equivalents were calculated using ratios from Minzenberg, Poole, Benton, and Vinogradov (2004) in which the average anticholinergic activity (as determined by binding affinity gathered from published studies reporting *in vitro* brain muscarinic receptor antagonism) of a medication was compared with that of benztropine (1mg) to determine a pharmacological index. Each patient's medication dosages were multiplied by this index to generate a total for each patient. Chlorpromazine equivalents for paliperidone and molindone, unavailable in the two previous studies, were calculated using beginning dosage information from the respective manufacturers. Neither drug exhibits appreciable affinity for muscarinic receptors (Janicak & Winans, 2007; Richelson & Nelson, 1984).

Measures

The National Institute of Mental Health (NIMH) designed the MATRICS initiative to support pharmacological treatment of cognitive deficits in schizophrenia. One goal for this consensus battery of cognitive tests was to permit comparisons across medication trials. The MATRICS Neurocognition Committee selected 10 tests that demonstrated similar effects among 5 study sites, high test-retest reliability, utility as a repeated measure, relationship to functional outcome, and practicality and tolerability (Neuchterlein et al., 2008). These tests cover seven domains of cognition: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition (determined to be

replicable across studies and represent fundamental dimensions of cognitive deficit in schizophrenia [Neuchterlein et al., 2004]). This MATRICS Consensus Cognitive Battery (MCCB) (Neuchterlein et al., 2008; Kern et al., 2008) has been used in large multi-site trials (Keefe et al., 2011) and has been shown to be a sensitive tool for assessing the extent of cognitive impairment in schizophrenia (August, Kiwanuka, McMahon, & Gold, 2012).

In the current study trained psychometricians administered the MCCB to participants at intake and at each follow-up visit.

Analytic Strategy

Baseline characteristics were examined to evaluate the distribution on demographic and clinical variables, as well as the medication status and performance on MATRICS battery. The correlation of chlorpromazine and benztropine values with overall composite t-scores on the MCCB at baseline was examined using Spearman's rho, as the data are were not normally distributed. Based on the findings of Vinogradov et al. (2009), additional correlations were calculated to evaluate correlations between benztropine/chlorpromazine loads and both t-scores and raw scores of the MCCB subtests. Finally, independent *t*-tests were used to determine whether subjects in the highest quartiles on chlorpromazine and benztropine levels had greater cognitive impairment than those in the lowest quartiles as evidenced by lower scores on the Hopkins Verbal Learning Test (HVLT) and the Letter Number Span (LNS) test, MCCB subtests of verbal learning and working memory, respectively. P value was set at 0.05 for all tests, using two-tailed tests.

Results

Table 1 shows the demographic information on the participants included in this secondary analysis. *T*-tests were run comparing demographic variables: male versus female

participants, paranoid schizophrenia versus all other participant diagnoses, African-American versus all other participant ethnicities, and single status versus all other participant marital statuses. No significant difference emerged with exception of comparisons of African-American participants versus the other samples. For example, the chlorpromazine load for African-American subjects (m = 520.33 ± 435.15) was significantly higher than that of the other subjects (m = 321.98 ± 228.27), $t(83.95) = -2.86$, $p < .05$. Although it was interesting that this population also had lower benztropine equivalents (m = 4.05 ± 12.77) than the rest of the participants (m = 11.09 ± 21.34), this difference was not statistically significant, $t(59.34) = 1.86$, $p > .05$. Comparisons of the mean t-scores of the MCCB tests demonstrated significant differences between ethnicities. On the overall composite score African-American participants had a mean score of 24.17 ± 10.91 compared to 32.78 ± 12.53 for the other ethnicities, $t(92) = 3.55$, $p < .05$. On the HVLT test African-American participants had a mean score of 33.83 ± 6.95 compared to 37.83 ± 8.47 for the other ethnicities, $t(92) = 2.51$, $p < .05$. On the LNS test African-American participants had a mean score of 33.37 ± 12.06 compared to 41.63 ± 10.38 for the other ethnicities, $t(92) = 3.48$, $p < .05$. Table 2 displays further clinical characteristics of the entire sample.

Of the 94 total patients, 88 were on antipsychotic medications, and 60 patients were on medications with demonstrable anticholinergic activity. Table 3 lists all medications prescribed to the participants, the number of milligrams of that medication equal to 100mg of chlorpromazine and 1mg of benztropine (where applicable), as well as the number of patients in the study on each drug. Each patient had an MCCB composite score as well as individual raw scores and t-scores for each of the subtests. When we compared the anticholinergic load to our patients' scores on cognitive tests, we found no significant correlation with global cognition, the

t-scores, or the raw scores of any subtest. We also found no significant correlation between any cognitive scores and our patients' chlorpromazine equivalents. Spearman correlations and their significance are shown in Tables 4 and 5.

Figures 1 and 2 show the distribution of the participants chlorpromazine and benztropine loads. The data are not normally distributed, and many patients were in the lower end (smaller daily dose equivalents) for both chlorpromazine and benztropine. We compared the mean scores on the HVLT and LNS of those patients in the highest quartile to those in the lowest quartile for both chlorpromazine and benztropine. Those two subtests were chosen as we would expect to see the largest anticholinergic effect on the domains of verbal learning and working memory.

The independent-samples *t*-test comparing the mean HVLT t-score in subjects in the highest chlorpromazine quartile (m = 35.00 ± 8.71) to the mean HVLT t-score of subjects in the lowest chlorpromazine quartile (m = 37.42 ± 7.44) found no significant difference, $t(45) = 1.024$, $p > .05$. Another independent-samples *t*-test was calculated to compare the mean LNS t-scores of subjects in the highest and lowest chlorpromazine quartiles. No significant difference was found, $t(45) = 1.692$, $p > .05$. The mean scores of the highest quartile (m = 40.54 ± 11.47) were not significantly different from those of the lowest quartile (m = 34.43 ± 13.24).

Likewise, an independent-samples *t*-test was calculated comparing the mean HVLT t-score of subjects in the highest benztropine quartile (m = 34.70 ± 8.13) to the mean HVLT t-score of subjects in the lowest benztropine quartile (m = 36.82 ± 8.41). Again, no significant difference emerged, $t(58) = .987$, $p > .05$. Another independent-samples *t*-test was calculated to compare the mean LNS t-scores of subjects in the highest and lowest benztropine quartiles. No significant difference was found, $t(58) = 1.048$, $p > .05$. The mean scores of the highest quartile

(m = 35.81 ± 10.80) were not significantly different from those of the lowest quartile (m = 38.91 ± 11.78).

Discussion

Of the 94 subjects in this sample, 88 had data on drug treatment and cognitive test performance. There were not significant differences in test scores or medication loads based on any demographic variables, with the exception of African American participants having higher chlorpromazine equivalents, lower composite scores, and lower HVLT and LNS t-scores than participants of other ethic groups. Subjects in this sample of all demographic variables were on a range of antipsychotic medications and other agents that contributed to a wide range of anticholinergic load. Our results show weak correlations between anticholinergic burden and MCCB scores at baseline (before cognitive intervention). In addition, *t*-tests comparing HVLT and LNS mean t-scores of those with the highest and lowest anticholinergic burden showed no statistical difference. Nor was there a significant relationship between the total chlorpromazine equivalents of patients' medication regimens and their performance on these same cognitive tests. These findings are not consistent with those of Vinogradov et al. (2009) who found that anticholinergic activity impaired cognitive performance in working memory and verbal learning and memory. In contrast to Vinogradov et al., who used a radioreceptor binding assay to determine serum anticholinergic activity, our equivalences were determined using estimations of anticholinergic activity based on prescribed medications. In the absence of blood levels, we cannot be certain that subjects were taking those medications as prescribed. However, our results are also inconsistent with those of Minzenberg et al. (2004) who used similar methods to determine the pharmacological indices. In that study, Minzenberg et al. observed that greater

anticholinergic burden was associated with greater impairment in attention and declarative memory.

Furthermore, we only have information on psychotropic medications, where patients may have been taking other non-psychiatric prescriptions or over the counter drugs that could have affected muscarinic receptors in the central nervous system. For this preliminary study, we did not control for age, duration of illness or level of education, all of which could affect cognitive abilities. We did not specifically control for IQ, but there is evidence that the summary of MCCB tests overlap with general intelligence (August et al., 2011). Although we did not find an association between cognition and chlorpromazine equivalent, we did not specifically control for symptom severity.

Similar to the findings of Vinogradov et al. and Minzenberg et al., our findings did not show a correlation between anticholinergic load and general cognition at baseline. In Vinogradov's study, however, anticholinergic load had a greater contribution to variance in the response of the subjects to change in cognition after remediation than to variance in baseline cognitive performance. This indicates the possibility that anticholinergic burden has a more pronounced influence on the effects of cognitive remediation rather than on cognition at baseline, which could be examined in future research. Our current results suggest, however, that the anticholinergic activity in psychiatric medications currently prescribed to this patient population may not significantly contribute to patients' current cognitive deficits. However, this was a relatively small, highly selected sample. Thus, these findings are vulnerable to a spurious finding of no difference.

References

Andreasen, N. C., Pressler, M., Nopoulos, P., Miller, D., & Ho, B. (2010). Antipsychotic dose equivalents and dose-years: A standardized method for comparing exposure to different drugs. *Biological Psychiatry, 67*(3), 255-262.

August, S. M., Kiwanuka, J. N., McMahon, R. P., & Gold, J. M. (2012). The MATRICS consensus cognitive battery (MCCB): Clinical and cognitive correlates. *Schizophrenia Research, 134*(1), 76-82.

Brebion, G., Bressan, R. A., Amador, X., Malaspina, D., & Gorman, J. M. (2004). Medications and verbal memory impairment in schizophrenia: The role of anticholinergic drugs. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences, 34*(2), 369-374.

Campbell, N., Boustani, M., Limbil, T., Ott, C., Fox, C., Maidment, I., . . . Gulati, R. (2009). The cognitive impact of anticholinergics: A clinical review. *Clinical Interventions in Aging, 2009:4*, 225-233.

Fumagalli, F., Frasca, A., Racagni, G., & Riva, M. A. (2009). Cognitive effects of second-generation antipsychotics: Current insights into neurochemical mechanisms. *CNS Drugs, 23*(7), 603-614.

Goldberg, T. E., & Green, M. F. (2002). Neurocognitive functioning in patients with schizophrenia: An overview. In K. L. Davis, D. Charney, J. T. Coyle & C. Nemeroff (Eds.), *Neuropsychopharmacology: The fifth generation of progress* (pp. 657-669). US: Lippincott Williams & Wilkins Publishers.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *The American Journal of Psychiatry*, 153(3), 321-330.

Janicak, P. G., & Winans, E. A. (2007). Paliperidone ER: A review of the clinical trial data. *Neuropsychiatric Disease and Treatment, 3*(6), 869-883.

Keefe, R. S. E., Fox, K. H., Harvey, P. D., Cucchiaro, J., Siu, C., & Loebel, A. (2011). Characteristics of the MATRICS consensus cognitive battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophrenia Research, 125*(2-3), 161-168.

Kern, R. S., Gold, J. M., Dickinson, D., Green, M. F., Nuechterlein, K. H., Baade, L. E., . . . Marder, S. R. (2011). The MCCB impairment profile for schizophrenia outpatients: Results from the MATRICS psychometric and standardization study. *Schizophrenia Research, 126*(1–3), 124-131.

Kern, R. S., Nuechterlein, K. H., Green, M. F., Baade, L. E., Fenton, W. S., Gold, J. M., . . . Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 2: Co-norming and standardization. *The American Journal of Psychiatry, 165*(2), 214-220.

Klinkenberg, I., & Blokland, A. (2010). The validity of scopolamine as a pharmacological model for cognitive impairment: A review of animal behavioral studies. *Neuroscience and Biobehavioral Reviews, 34*(8), 1307-1350.

Kurtz, M. M., Wexler, B. E., Fujimoto, M., Shagan, D. S., & Seltzer, J. C. (2008). Symptoms versus neurocognition as predictors of change in life skills in schizophrenia after outpatient rehabilitation. *Schizophrenia Research, 102*(1-3), 303-311.

Minzenberg, M. J., Poole, J. H., Benton, C., & Vinogradov, S. (2004). Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. *The American Journal of Psychiatry, 161*(1), 116-124.

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research, 72*(1), 29-39.

Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., . . . Marder, S. R. (2008). The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *The American Journal of Psychiatry, 165*(2), 203-213.

O'Carroll, R. (2000). Cognitive impairment in schizophrenia. *Advances in Psychiatric Treatment*, *6*(3), 161-168.

Ozbilen, M., & Adams, C. E. (2009). Systematic overview of Cochrane reviews for anticholinergic effects of antipsychotic drugs. *Journal of Clinical Psychopharmacology, 29*(2), 141-146.

Richelson, E., & Nelson, A. (1984). Antagonism by neuroleptics of neurotransmitter receptors of normal human brain in vitro. *European Journal of Pharmacology, 103*(3–4), 197-204.

Shamsi, S., Lau, A., Lencz, T., Burdick, K. E., DeRosse, P., Brenner, R., . . . Malhotra, A. K. (2011). Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophrenia Research, 126*(1-3), 257-264.

Sharma, T., & Antonova, L. (2003). Cognitive function in schizophrenia: Deficits, functional consequences, and future treatment. *Psychiatric Clinics of North America, 26*(1), 25-40.

Surti, T. S., Corbera, S., Bell, M. D., & Wexler, B. E. (2011). Successful computer-based visual training specifically predicts visual memory enhancement over verbal memory improvement in schizophrenia. *Schizophrenia Research, 132*(2-3), 131-134.

Velligan, D. I., & Miller, A. L. (1999). Cognitive dysfunction in schizophrenia and its importance to outcome: The place of atypical antipsychotics in treatment. *Journal of Clinical Psychiatry, 60*(Suppl 23), 25-28.

Velligan, D. I., Prihoda, T. J., Sui, D., Ritch, J. L., Maples, N., & Miller, A. L. (2003). The effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings. *Journal of Clinical Psychiatry, 64*(5), 524-531.

Vinogradov, S., Fisher, M., Warm, H., Holland, C., Kirshner, M. A., & Pollock, B. G. (2009). The cognitive cost of anticholinergic burden: Decreased response to cognitive training in schizophrenia. *The American Journal of Psychiatry, 166*(9), 1055-1062.

Weiss, E. M., Bilder, R. M., & Fleischhacker, W. W. (2002). The effects of second-generation antipsychotics on cognitive functioning and psychosocial outcome in schizophrenia. *Psychopharmacology, 162*(1), 11-17.

Zink, M., Englisch, S., & MeyerLindenberg, A. (2010). Polypharmacy in schizophrenia. *Current Opinion in Psychiatry, 23*(2), 103-111.

Table 1

Demographic Characteristics of 94 Study Participants

Variable	N	%
Gender		
Male	54	57.4
Female	40	42.6
Diagnosis		
Schizophrenia, Paranoid	40	42.6
Schizophrenia, Disorganized	1	1.1
Schizophrenia, Residual	13	13.8
Schizophrenia, Undifferentiated	11	11.7
Schizoaffective Disorder	29	30.9
Ethnicity		
African-American	54	57.4
Caucasian	38	40.4
Hispanic	1	1.1
Other	1	1.1
Marital Status		
Single	77	81.9
Married	5	2.9
Separated/Divorced	11	11.7
Widowed	1	1.1

Table 2
Clinical Characteristics of 94 Study Participants

Variable	Mean	SD	Range
Age	43.00	10.23	23 – 64
Education (years)	12.70	2.43	8 – 25
Duration of Illness (years)	21.49	12.06	1 – 50
PANSS Positive Score	13.86	7.07	2 – 33
PANSS Negative Score	13.16	7.03	1 – 29
PANSS General Score	25.97	11.88	1 – 47
Benztropine Equivalent	7.05	17.21	.00 – 77.00
CPZ Equivalent	435.93	373.48	.00 – 2272.73
HVLT t-score	35.44	7.71	23 – 60
LNS t-score	36.58	11.99	0 – 64

Table 3

Benztropine and Chlorpromazine Equivalents in Study Subjects at Baseline

Medication	Benztropine[a]	Chlorpromazine[b]	#ofPts[c]
Antipsychotics			
Aripiprazole (Abilify)	6.42	_	14
Clozapine (Clozaril)	8	108	13
Olanzapine (Zyprexa)	17	4.75	14
Risperidone (Risperdal)	_	1.32	14
Quetiapine (Seroquel)	733	142	11
Ziprasidone (Geodon)	_	50.5	8
Haloperidol (Haldol)	_	1.84	4
Chlorpromazine (Thorazine)	47	100	1
Perphenazine (Trilafon)	1470	6.9	8
Fluphenazine (Prolixin)	_	1.76	3
Paliperidone (Invega)	_	6	1
Molindone (Moban)	_	50	1
Fluphenazine Decanoate (mg/2-3wks)	_	7.91	6
Haloperidol decanoate (mg/4 wks)	_	35.3	2
Risperdal Consta (mg/2wks)	_	25	5
Antidepressants			
Paroxetine (Paxil)	73	_	3
Sertraline (Zoloft)	490	_	4
Anti-parkinsonian agents			
Benztropine (Cogentin)	1	_	23
Diphenhydramine (Benadryl)	147	_	1
Trihexyphenidyl (Artane)	1.6	_	3

[a]Benztropine 1mg is equal to the number of milligrams listed for each drug
[b]Chlorpromazine 100mg is equal to the number of milligrams listed for each drug
[c]Total number of participants for whom each drug was prescribed

Table 4
Spearman Correlations Between Cognitive Test T-Scores and Medication Equivalents

MCCB[a] Test	Benztropine rho (p value)	Chlorpromazine rho (p value)
Composite Score	-0.119 (0.255)	-0.145 (0.163)
Trail-Making	-0.172 (0.098)	-0.045 (0.665)
Symbol Coding	0.014 (0.897)	-0.150 (0.149)
Hopkins Verbal Learning Test	-0.133 (0.201)	-0.085 (0.416)
Spatial Span	-0.027 (0.795)	-0.075 (0.473)
Letter-Number Span	-0.104 (0.320)	-0.163 (0.116)
Mazes	-0.103 (0.321)	0.028 (0.789)
Brief Visual-Spatial Memory Test	-0.085 (0.413)	-0.121 (.245)
Category Fluency	0.092 (0.380)	-0.062 (0.555)
Managing Emotions	-0.124 (0.233)	-0.106 (0.311)
Continuous Performance Test	-0.051 (0.625)	-0.145 (0.162)

[a]MCCB =MATRICS Consensus Cognitive Battery

Table 5

Spearman Correlations Between Cognitive Subtest Raw Scores and Medication Equivalents

MCCB[a] Test	Benztropine rho (p value)	Chlorpromazine rho (p value)
Trail-Making	0.157 (0.130)	-0.002 (0.987)
Symbol Coding	0.044 (0.673)	-0.057 (0.588)
Hopkins Verbal Learning Test	-0.127 (0.223)	-0.078 (0.453)
Spatial Span	-0.011 (0.914)	-0.009 (0.932)
Letter-Number Span	-0.093 (0.374)	-0.133 (0.200)
Mazes	-0.050 (0.634)	0.124 (0.234)
Brief Visual-Spatial Memory Test	-0.042 (0.690)	-0.011 (.917)
Category Fluency	0.099 (0.344)	-0.037 (0.722)
Managing Emotions	-0.123 (0.237)	-0.117 (0.262)
Continuous Performance Test	-0.032 (0.760)	-0.106 (0.307)

[a]MCCB =MATRICS Consensus Cognitive Battery

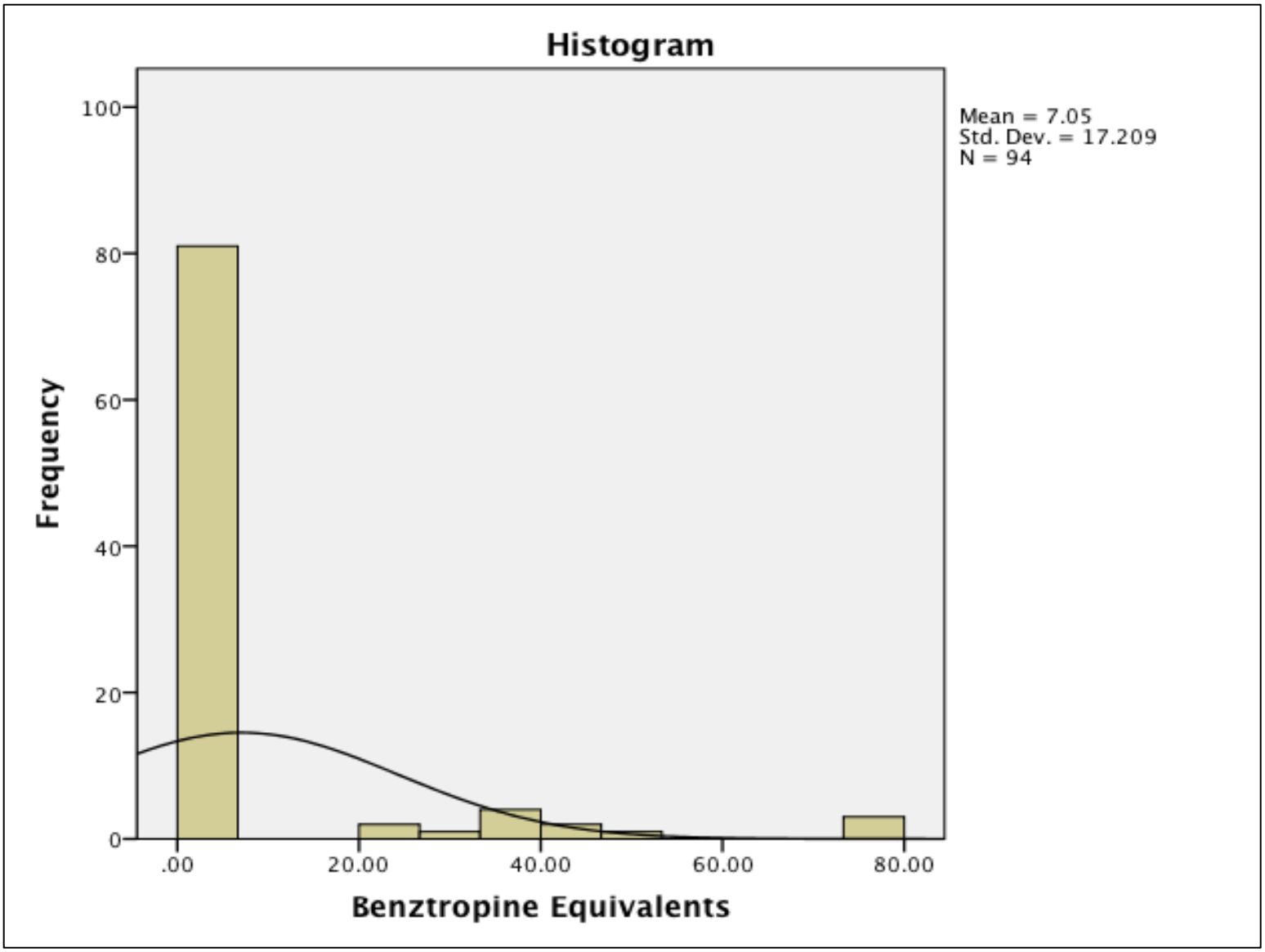

Figure 1. Distribution of the frequencies of participant total benztropine loads

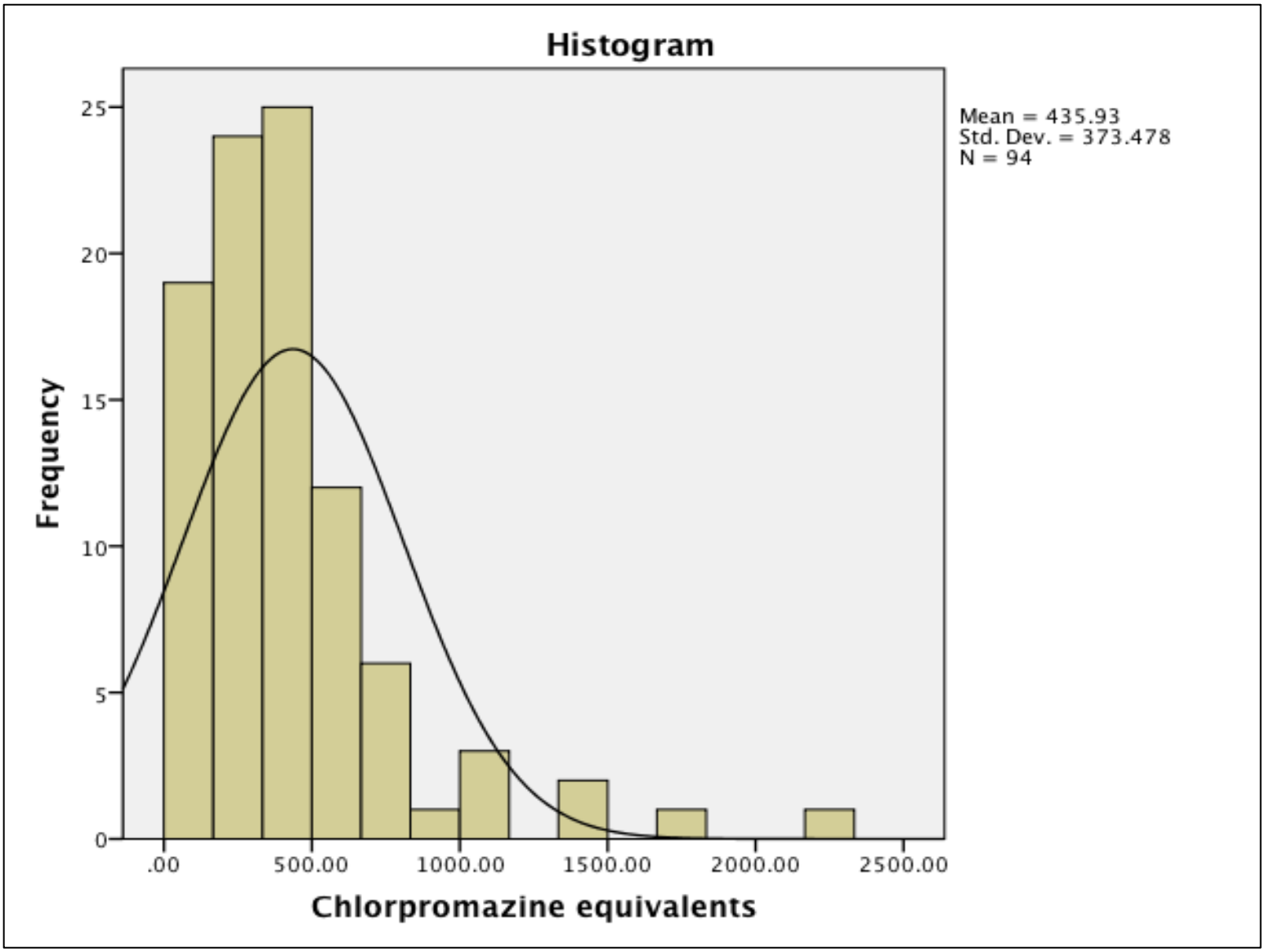

Figure 2. Distribution of the frequencies of participant total chlorpromazine loads