A META-ANALYSIS OF NEUROPSYCHOLOGICAL CHANGE TO CLOZAPINE, OLANZAPINE, QUETIAPINE, AND RISPERIDONE IN SCHIZOPHRENIA

By

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To my parents.

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LIST OF TABLES

LIST OF FIGURES

TABLE OF CONTENTS

CHAPTER I

INTRODUCTION

Cognitive dysfunction is fundamental to schizophrenia (Kraepelin & Robertson, 1971; Blueler, 1905) and readily demonstrated on a variety of neuropsychological instruments (Kolb & Whishaw, 1983). Patients with schizophrenia typically perform one to two standard deviations below normal on a variety of measures; especially those that assess executive functions, verbal skills, processing speed, and attention (Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992; Saykin et al., 1994; Bilder et al., 2000; Fuller et al., 2002; Heinrichs & Zakzanis, 1998). Cognitive impairment in schizophrenia relates directly to socio-vocational functioning (Green, Kern, Braff, & Mintz, 2000; Green, 1996), and has been reported to exert a greater influence on functional outcome than the presence or severity of the positive or negative symptoms of schizophrenia (Velligan, Bow-Thomas, Mahurin, Miller, & Halgunseth, 2000). A recent review and meta-analysis delineated the direct associations between neuropsychological functions and dimensions of outcome (Green et al., 2000). Executive skill (i.e. WCST), secondary verbal memory, and verbal fluency were associated with community/daily living skills. Secondary verbal memory and vigilance were related to social problem solving/instrumental skills. Immediate and secondary verbal memory were associated with psychosocial skill acquisition. An improvement in cognitive skill may thus have important consequences for rehabilitation, and the elucidation of particular associations between cognitive impairments and psychosocial limitations may provide a framework for the prediction of functional changes resulting from treatment-specific changes in cognitive status.

With few exceptions, deficits on neuropsychological tests do not respond to treatment with first generation antipsychotics (FGAs). Subtle and equivocal benefits from FGAs have been demonstrated on measures of attention (e.g. CPT, Digit Span), but no consistent changes have been reported on measures of general intellect, verbal skills, visual skills, executive skills, immediate recall or delayed recall (Spohn, Lacoursiere, Thompson, & Coyne, 1977; Spohn & Strauss, 1989; Blyler & Gold, 2000). In fact, there is speculation that FGAs may have deleterious effects on specific cognitive skills, such as fine motor skill and procedural learning, deficits that presumably result from pharmacological blockade of D2 receptors at the dorsal

striatum (Blyler & Gold, 2000; Purdon, Woodward, Mintz, & Labelle, 2002; Purdon, Woodward, Lindborg, & Stip, 2003; Stevens et al., 2002; Bedard, Scherer, Delorimier, Stip, & Lalonde, 1996; Bedard et al., 2000; Saint-Cyr, Taylor, & Lang, 1988; Farde et al., 1992; Kapur, Zipursky, & Remington, 1999). Thus in some cognitive domains, traditional antipsychotics may not only fail to improve cognitive performance, but may actually lead to greater impairments (Carpenter & Gold, 2002).

A body of evidence has begun to accumulate that suggests potential cognitive benefits from SGAs (e.g. Galletly, Clark, McFarlane, & Weber, 1999; Buchanan, Holstein, & Breier, 1994; Bilder et al., 2002; Purdon, Malla, Labelle, & Lit, 2001). The apparent cognitive enhancements may relate to the novel pharmacological properties of SGAs, such as a lower affinity for dorsal striatal D2 receptors and greater seretonergic activity relative to FGAs (Kapur et al., 1999; Kapur & Seeman, 2001; Kapur & Remington, 2001). While the former attribute likely underlies the reduced propensity of SGAs to induce EPS and procedural learning impairment, the latter might explain the cognitive advantages of SGAs over FGAs (Meltzer, 1999; Chaudhry, Soni, Hellewell, & Deakin, 2002). Pharmacological differences within the SGA class may also suggest dissociable effects on cognition. For example, cholinergic inhibition adversely affects cognitive skills, particularly attention and memory (Bartus & Johnson, 1976; Frith, 1984; Spohn et al., 1989), and SGAs demonstrate variability in their degree of anticholinergic action. Both olanzapine and clozapine have significant anticholiergic activity and, therefore, may not improve aspects of attention and memory to the same degree as risperidone and quetiapine. This may be particular relevant to clozapine since it is typically prescribed at much higher doses despite having equivalent muscarinic receptor affinity as olanzapine (Lavalaye, Booij, Linszen, Reneman, & van Royen, 2001; Richelson & Souder, 2000; McGurk & Powchick, 2000). Similarly, within the SGA class, risperidone has a relatively high affinity and long dissociation latency period for D2 receptors (Lavalaye et al., 1999; Seeman, 2002), suggesting that patients receiving risperidone may be more likely to display adverse effects associated with dopamine antagonism in the striatum including greater EPS symptoms and reduced procedural learning. A recent meta-analysis of EPS prevalence in clinical trials and preliminary evidence of reduced procedural learning with risperidone, relative to clozapine and olanzapine, provide support for this prediction (Leucht, Pitschel-Walz, Abraham, & Kissling, 1999; Bedard et al., 2000; Purdon et al., 2003). If EPS or procedural learning effects influence

performance on other cognitive domains, risperidone may produce a unique profile of neuropsychological benefits relative to other SGAs.

Although important to rehabilitation, the significant methodological differences that exist across studies undermine attempts to draw definitive conclusions on the efficacy and differential benefits of SGAs to cognition in schizophrenia. Two earlier quantitative reviews of published studies up to 1998 identified significant gains with SGAs in several cognitive domains including verbal fluency, vigilance, secondary memory, and visuomotor skills (Keefe, Silva, Perkins, & Lieberman, 1999; Harvey & Keefe, 2001). Effect sizes, in terms of Cohen's d, were typically within the range of 0.2 to 0.4 suggesting that the improvements may have limited clinical significance. However, these earlier reviews were hampered by the relatively small number of double blind, random assignment studies that had been carried out prior to 1998, limited availability of data on olanzapine, and complete absence of data on quetiapine. Since 1998 the results of over 20 studies involving SGAs including several large scale NIMH and industry sponsored clinical trails have been released and there is now a substantial pool of data on olanzapine's effects on cognition and results from several investigations of quetiapine (Bilder et al., 2002; Harvey, Green, McGurk, & Meltzer, 2003; Purdon et al., 2001; Velligan et al., 2002).

The larger number of studies now available for review permits a more thorough investigation of the cognitive improvements associated with SGAs. Specifically, enough studies now exist to allow an identification of potential differences between treatments. Although several investigations have directly compared medications within the SGA class, with few exceptions, (e.g. Harvey et al., 2003), interpretation of the results have been limited by the small number of subjects included in treatment groups (Purdon et al., 2000; Bilder et al., 2002). By quantitatively analysing effects across studies, meta-analysis may help to overcome these sample size limitations, and help identify possible differences between treatments with respect to their effects on cognition.

The large number of studies that have been reported since 1998 also make it feasible to examine the effects of relevant methodological characteristics, such as medication blind, random assignment of subjects, and study duration. Earlier reviews have stressed the importance of controlling for these variables to protect against experimenter bias and demand characteristics. However, quantitative comparisons between studies that included these design features and those that did are lacking.

A meta-analysis of SGA studies may also be useful for addressing issues associated with baseline medications status and practice effects. Several investigators have speculated that the cognitive improvements observed with SGAs may, in part, represent practice effects associated with repeated exposures to neuropsychological test batteries and an avoidance of derogatory effects associated with FGAs (Carpenter et al., 2002; Purdon et al., 2002; Purdon et al., 2003; Tandon, Milner, & Jibson, 1999). Specifically, several FGA vs. SGA clinical trials have been criticized for using doses within the FGA arm that are too high, thus impairing cognition within the FGA comparator arm, or at least limiting the degree of improvement expected from retesting alone, and falsely identifying gains with SGAs, that presumably do not have similar negative effects on cognition. In the case of within subjects switch studies, the absence of an unmedicated baseline assessment does not rule out a similar possibility that the improvements observed following a switch to an SGA treatment reflect a release from the adverse effects associated with FGAs rather than a novel enhancement of cognition. Support for these contentions comes from a recent two-year investigation of risperidone versus low dose haloperidol (Green et al., 2002) and repeated demonstrations of a complete absence of improvement in the FGA comparator arms of several recent clinical trials (Bilder et al., 2002; Purdon et al., 2000).

At present, over 40 studies have reported on the effects of clozapine, olanzapine, risperidone and quetiapine on a wide range of neuropsychological tests. The studies were entered into a meta-analysis to (1) evaluate and extend the findings of the earlier meta-analyses, (2) identify any differences between SGA medications on cognitive processes, (3) identify study characteristics that might be relevant to demonstrations of cognitive change, and (4) attempt to demarcate the cognitive benefits of SGAs, if they exist, from those that might be attributed to practice effects.

CHAPTER II

METHODS

Literature Search

Relevant articles were identified through extensive literature searches of computerized databases including PsycInfo, Medline, and Dissertation Abstracts. Key search terms included Schizophrenia, Cognition, Neuropsychology, Neurocognition, Clozapine, Olanzapine, Risperidone, and Quetiapine. In addition, the bibliographies of several earlier reviews were examined (Keefe et al., 1999; Meltzer & McGurk, 1999; Purdon, 1999; Purdon, 2000; Harvey et al., 2001). To ensure that the most recently published articles were included, the online table of contents and upcoming articles sections of the *American Journal of Psychiatry*, *Archives of General Psychiatry*, *Biological Psychiatry*, *British Journal of Psychiatry*, *Schizophrenia Research*, *Neuropsychopharmacology*, and *Psychopharmacology* web sites were reviewed for relevant articles. Also, the authors of abstracts pertaining to cognition and treatment presented at the most recent international conference devoted to schizophrenia research (Schizophrenia Research, 2002) were contacted to solicit preprints of manuscripts accepted for publication but not yet in print.

Studies were included in the current meta-analysis if they met the following criteria: 1) inclusion of patients with a diagnosis of schizophrenia or schizoaffective disorder as outlined in DSM-III, DSM-III-R, DSM-IV, or ICD-9, ICD-10; 2) prospective study design with a baseline assessment and at least one follow-up assessment; 3) trial duration of at least 1 week; 4) no antipsychotics, aside from the study medications were administered; 5) a baseline sample size of at least 10; 6) results of neuropsychological change to treatment were reported for at least one of the common tests listed in Table 1; and 7) the study was published or 'in press' in a peer reviewed journal. Investigations of geriatric, adolescent (age <18 yrs), or high-risk populations were not included.

Coding of Study Characteristics

Studies were coded for author and year of publication, schizophrenia sub-type classification, baseline medication status, medication blind, random assignment, trial

medications, total subjects enrolled and the number completing the trial, trial duration, use of alternate neuropsychological test forms when applicable, and mean trial medication dosages.

Schizophrenia sub-type classification was based on explicit descriptions contained in each publication and consisted of three classifications: general schizophrenia, early phase, or treatment refractory. Medication blind was coded as double blind or open label. Open label extensions to double blind studies were not included in this analysis with one exception (Smith et al., 2001) because the within-group results were not reported for the end of the double-blind phase. The number of subjects who completed the study was defined as the total number of subjects that completed the trial. In addition, if a study reported statistics based on the last-observation-carried-forward (locf) method, then these values were used to calculate effect sizes and the number of subjects completing at least one follow-up assessment was also reported.

Neuropsychological tests and Domains

An earlier meta-analysis of neurocognitive deficits in schizophrenia calculated effect sizes for individual neuropsychological tests rather than combining tests into domain scores (Heinrichs et al., 1998). For comparison purposes, the same method was utilized in the current set of meta-analyses, although in several cases highly similar tests were combined into a single measure (e.g. verbal list learning). In addition, composite domains scores have also been calculated by averaging effect sizes within studies across tests that putatively tap similar skills. Thus, each study contributed at least one effect size for each neuropsychological test and cognitive domain. Both the effect sizes for the domains and individual tests are reported. The construction of the domains reported here was based upon prior reviews and earlier studies that utilized large cognitive batteries, contemporary neuropsychological domain constructs, and cognitive domains identified as being especially relevant to outcome in schizophrenia (Purdon et al., 2000; Purdon et al., 2001; Green et al., 2002; Bilder et al., 2002; Heaton et al., 2001; Harvey & Keefe, 2001). The tests and domains are listed in Table 1.

The Vigilance domain included the Continuous Performance/Attention Test (CPT), Stroop Test (Stroop color-word), and Trailmaking A Test (TMA). An aggregate score across both visual and auditory test versions was used for the CPT score. This domain is linked to several dimensions of outcome (Green et al., 2000).

The Working Memory domain consisted of the Verbal Working Memory and Spatial Working Memory scores. The Verbal Working Memory measure included the Digit Span, Digit Span Distraction, Paced Auditory Serial Addition, Letter-Number Span, and Consonant Trigrams tests. The Spatial Working Memory measure included the Visual Span subtest of the WAIS-R/III and the Spatial Working Memory Test (Meltzer et al., 1999; Green et al., 2002; Harvey et al., 2003).

The Learning domain consisted of the Rey Serial Design Learning Test (RDLT), paragraph recall tests (LM I; WMS-R/III Logical Memory I or the Story Recall Test), verbal list learning tests (VLL I; California, Crawford, Hopkins or Rey Verbal Learning tests, or the Bushcke Selective Reminding Test), and visual reproduction tests (VR I; WMS-R/III Visual Reproduction subtest, the Rey-Osterith/Taylor Complex Figure Test, or the Benton Visual Retention Test).

The Cognitive Flexibility & Abstraction domain consisted of the WCST (perseverate errors or percent perseverative errors score) and the WAIS-R/III Similarities subtest.

The Processing Speed domain included the Digit Symbol/Modalities Test, Trailmaking B (TMB), and the Wechlser Intelligence Scale for Children-Revised/III (WISC-R/III) Mazes subtest. This domain is associated with several dimensions of outcome.

The Verbal Fluency domain consisted of a single measure that was calculated by combining the Controlled Oral Word Association and Category Instance Generation tests. Verbal Fluency is strongly correlated with outcome measures of community/daily activities.

The Visuospatial Processing domain included the WAIS-R Block Design subtest (BD), the Rey-Osstereith/Taylor Complex Figure Test copy score (CFTc) and a visual organization (VOT) score derived from either the Hooper Visual Organization Test, Mooney Face Closure Test, Benton Judgment of Line Orientation, or Line Drawing tests.

The Motor Skill Domain included the Finger Tapping Test (FTT) and a manual dexterity score consisting of either the Grooved Pegboard Test or the Pin Test (GPB/PIN).

The Delayed Recall domain included a visual recall score (VR II; WMS-R Visual Reproduction II or the delayed RCFT), a verbal recall score (LM II; WMS-R Logical Memory II or the delayed Story Recall Test), and a verbal list learning score (VLL II; delayed free recall scores from the verbal list learning tests described above).

Calculation of Effect Sizes and Data Analysis

Typically, meta-analyses only include double-blind studies that randomly assigned subjects to either a control group or an active treatment group. However, this approach would overlook a substantial body of evidence from open-label and single sample studies that may be relevant to the demonstration of cognitive change from SGA treatments. In an attempt to preserve scientific rigor without omitting potentially important results, two analyses were undertaken, the first with a conservative approach to the published literature and the second with less conservative restrictions.

Analysis One

The first analysis included only reports from double-blind comparisons of FGAs and SGAs that randomly assigned patients to treatment. Hedges' g was used to estimate effect size by computing the difference between the post-treatment means of SGA and FGA groups, divided by their pooled standard deviation. Where group means and standard deviations were not explicitly reported, Hedges' g was calculated using appropriate alternative methods based on t or F statistics as outlined by Rosenthal (1994). Where the t or F statistics were also not reported, data were solicited from the original study authors. A weighted average effect size estimate was calculated for each neuropsychological test and domain by combining data from all studies that examined cognitive change to clozapine, olanzapine, risperidone, or quetiapine. In cases where a study included more than one SGA arm, in addition to an FGA control, or multiple dosing arms, the SGA arms were treated as separate samples and effect sizes for each arm were calculated. Effect sizes were combined according to the fixed effects model described by Shadish & Haddock (1994). Briefly, each effect size was weighted by the inverse of its associated variance such that effect sizes calculated from studies with larger sample sizes contributed more to the overall effect size when combined. A weighted average effect size and corresponding 95% confidence interval (CI) were then calculated. CI's that excluded zero were considered significant. Positive values indicate improvement and negative values indicate a decline in performance. To assess the relevance of predefined moderator variables, a measure of effect size homogeneity, the Q statistic, was also calculated for each neuropsychological domain. The Q statistic has a chi-square distribution with k-1 degrees of freedom, where k is the number of

effect sizes being combined. The critical alpha for the Q statistic was set at .05. When the assumption of homogeneity was rejected the effect sizes were combined using the random effects model and an analysis of moderator variables was undertaken (Hedges & Vevea, 1998). In the moderator variable analysis, the Q statistic was partitioned into a between groups component, Q_{BET}, and a within groups component, Q_W. A moderator variable was considered significant if it effectively separated the effect sizes into separate categories (i.e. Q_{BET} was significant) that did not have significant within group variation (i.e. Q_W was not significant). The R^2 value was also calculated for each significant moderator variable to assess the strength of the relationship between moderator and dependent variables. Moderator variables included the coded study characteristics of baseline medication status (medicated vs. unmedicated) and schizophrenia sub-type classification (early phase combined with general, vs. treatment refractory). In addition, Pearson's R correlations were carried out for each domain to examine possible relationships between effect sizes and trial duration or effect sizes and FGA comparator drug dose. To avoid violations of independence in the moderator variable analysis, average effect sizes were calculated across groups for the three studies that examined cognitive change in more than one SGA treatment or dosing arm (Bilder et al., 2002; Velligan et al., 2002; Purdon et al., 2000).

Analysis Two

The second analysis included all prospective studies of cognitive change that evaluated clozapine, olanzapine, risperidone, or quetiapine. The second analysis included all prospective studies, including both the double-blind and the open label studies, regardless of whether or not participants were randomly assigned to treatment. Investigations of cognitive change following a shift from one SGA to another were not included. A one sample, dependent measures index of effect size analogous to Hedges' g, the mean change score divided by its standard deviation, was used as the estimate of effect size (Rosenthal, 1994). Paired t-tests or alternative repeated measures values were available to calculate an effect size for the majority of studies. In studies that did not report change scores, an estimate of effect size was derived using the procedure of Smith, Glass, and Miller (1980), which estimates change from the pre-treatment and post-treatment group means, divided by the standard deviations reported in the original manuscript, and adjusted for test-retest correlations provided in a compendium of neuropsychological tests

(Spreen & Strauss, 1998). Weighted effect sizes, 95% CIs, and Q statistics were then calculated overall for each neuropsychological measure and domain, and again within each medication group. As in Analysis One, when the Q statistic was rejected, effect sizes were combined according to the random effects model.

The effect sizes obtained in Analysis Two were compared to effect sizes obtained from longitudinal studies of the stability of neuropsychological function in schizophrenia and controls in order to examine the contribution of practice effects to the improvements associated with SGA medications (Heaton et al., 2001; Sweeney, Haas, Keilp, & Long, 1991; Dikmen, Heaton, Grant, & Temkin, 1999; Basso, Bornstein, & Lang, 1999; Basso, Lowery, Ghormley, & Bornstein, 2001). These studies were used because a) they examined practice effects across test-retest intervals comparable to studies of SGAs (i.e. 6 to 18 months), b) included comprehensive test batteries that overlapped considerably with the tests examined in the current meta-analysis and provided enough data to calculate effect sizes, and c) included an appropriate number of subjects (range 39-384). In general, investigations of the longitudinal stability of neuropsychological deficits in schizophrenia have indicated that practice effects across repeated administrations of neuropsychological tests are very similar to those observed in healthy controls (e.g. Heaton et al., 2001; Hoff et al., 1999; Censits, Ragland, Gur, & Gur, 1997; Rund, 1998). The following practice related effect sizes were obtained from the above studies: Vigilance ES=0.27, Working Memory ES=0.12, Learning ES=0.32, Processing Speed ES=0.35, Cognitive Flexibility and Abstraction ES=0.27, Verbal Fluency ES=0.16, Visuospatial Skill ES=0.36, Motor Skill ES=0.15, Delayed Recall ES=0.20. These effect sizes were compared to those obtained from studies of SGAs and if the 95% CI identified for a given domain excluded the practice effect size, the improvement was considered significantly greater than that expected from practice alone.

Analysis Two had a sufficient number of studies to allow for a more comprehensive examination of the influence that study characteristics might have on effect sizes and comparisons between SGA medications. Comparisons of the dichotomous variables study blind or random assignment (controlled vs. uncontrolled), baseline medication status (unmedicated vs. medicated), and schizophrenia sub-type classification (early phase combined with general, vs. treatment refractory) were carried out as described in Analysis One (by partitioning the Q statistic into between and within groups components) for each cognitive domain. The variables

study blind and random assignment were collapsed into a single variable due to the fact that almost every study that was double blind also randomly assigned subjects to treatment. Thus, in order to avoid the redundancy of carrying out two comparisons, studies that included at least one of these features in their design were coded as controlled and those that did not include either were coded as uncontrolled. Pearson's R correlations were carried out to examine relationships between domain effect sizes and study duration.

In addition, contrasts between medication groups were carried out for each cognitive domain. Group differences were examined in the same manner as moderator variables, by partitioning the Q statistic into a between and within groups component where the between groups component reflects the difference between medication groups and the within groups component represents an overall measure of the variability within medication groups. In cases were Q_{BET} was significant, pairwise contrasts were carried out to identify specific differences between medication groups. A weighted within medication group effect size was not included in the pairwise contrasts if it was calculated under the random effects model.

CHAPTER III

RESULTS

Analysis One

Study Demographics

Twelve studies were included in analysis one. Effect sizes for one study could not be computed from the information provided by the author (Kern et al., 1998). Two studies included more than one SGA treatment arm (Purdon et al., 2000; Bilder et al., 2002) and one study randomized subjects to two separate dose groups of the same SGA treatment (Velligan et al., 2002). Schizophrenia sub-type classification for the 12 studies was early phase (n=1), general (n=5), and treatment refractory (n=6). Baseline medication status included unmedicated (n=4) and medicated (n=8). After excluding four reports from the same study because of discrepancies in the reported number of enrolled subjects (Green et al., 1997; Kern et al., 1998; Kern et al., 1999; McGurk et al., 1997), the eight remaining (independent) studies reported retention of 43% to 93% of the enrolled patients. As expected, attrition was lower in studies with a short duration of treatment and retention improved to a range of 55% to 93% of enrolled subjects when the last observation was carried forward for analysis.

Trial durations ranged from 4 weeks to 104 weeks and most studies included a variety of neuropsychological tests. Practice effects were relevant to instruments used in nine of the twelve studies, but only four of the nine included alternate forms in the experimental design ((Purdon et al., 2000; Purdon et al., 2001; Ljubin, Zakic, Mimica, Folnegovic-Smalc, & Makaric, 2000; Smith, Infante, Singh, & Khandat, 2001). The range of average doses used for each medication was consistent with doses recommended in the various product monographs; clozapine (410.5-498 mg), olanzapine (11-30 mg), risperidone (5.7-11.3 mg), and quetiapine (300-600 mg). The average dose used in the haloperidol control arms ranged from 4.5-37.9 mg.

Neuropsychological Test Effect Sizes

SGAs improved cognitive function more than FGAs in the Learning (ES=0.33), Processing Speed (ES=0.27), Verbal Fluency (ES=0.26), and Delayed Recall (ES=0.24) domains. Significant improvements were observed on all tests grouped within the Learning domain (ES=0.32-0.73), both tests of Processing Speed (DSST=0.41, TMB=0.19), and two tests

within the Delayed Recall domain (VLL II=0.35, VR II=0.31). Additional improvements on specific tests were observed within the Working Memory (Spatial Working Memory: ES=0.39) and Motor Skills (FTT: ES=0.30) domains (see Table 2). The assumption of homogeneity was not violated on any domain score and only one test, DSST, was calculated under the random effects model do to the presence of significant heterogeneity amongst the set of effect sizes that comprised the combined weighted effect size for this test, $?^2_{df=9}$=17.36, p=.027.

Study duration was significantly inversely correlated with the Learning and Cognitive Flexibility and Abstraction domain effect sizes, Pearson's r=-.87, p<.025, and r=-.92, r<.005 respectively. It was apparent however, that the correlations were heavily influenced by the Green et al. (2002) study that was considerably longer, 104 weeks, than the remaining studies. After removal of this study, a positive correlation between study duration and Cognitive Flexibility and Abstraction domain effect size was present, r=.90, p<.016. Comparator drug dose was not significantly correlated with any cognitive domain, however, the correlations for Vigilance, Learning, Cognitive Flexibility and Abstraction, and Processing Speed effect size were all greater than .63, p<.18, indicating that studies utilizing higher doses of haloperidol tended to produce larger SGA effect sizes for these domains.

Analysis Two

Study Demographics

Forty-one studies met the criteria for inclusion in analysis two. The schizophrenia sub-type classification included early phase (n=4), general (n=18), and treatment refractory (n=19) patients. Baseline medication status included unmedicated (n=11), medicated (n=29), and unknown (n=1). Eighteen studies randomly assigned patients to treatment arms and fifteen were double blind investigations. Two studies were single blind. Among the studies that were not included in Analysis One, the percentage of subjects completing the trials ranged from 45% to 100%. As expected the average percentage was high, 82%, possibly reflecting the tendency for less controlled studies to infrequently report the number of subjects initially screened or enrolled in a study. Follow-up assessments ranged from 1.5 weeks to 3 years and the size of the test batteries ranged from a single measure to 18 tests. Thirty-two studies used neuropsychological tests for which alternate forms were available, but only 11 of the 32 included alternate forms in the experimental design. The mean and range (in parentheses) of doses under double-blind (DB)

conditions tended to be lower than the open label (OL) doses in studies of clozapine: DB=454.3 (410.5-498), OL=459 (200-719), and quetiapine: DB=456.1 (300-600), OL=479.3 (319.3-750), whereas the reverse was true for olanzapine: DB =20.3 (11-30), OL=18 (12-35.5), and risperidone: DB=6.8 (5-11.3), OL =5.5 (2.2-8.95).

Neuropsychological Test Effect Sizes

Second Generation Treatments

The information provided by the authors of two studies was insufficient to allow calculation of effect sizes (Meltzer, 1992; Kern et al., 1998). The second analysis showed a more robust SGA benefit on cognitive skills than the more conservative first analysis (see Table 3). All cognitive domains demonstrated a substantial improvement on SGA medications compared to an FGA or medication free baseline. The weighted effect sizes for the nine domains ranged from 0.18 to 0.37. Similarly, significant improvements were observed on virtually every test and the effect sizes ranged from a low of 0.14 on the WCST to a high of 0.61 on the DSST. The weighted effect size for one domain, Vigilance, was calculated under the random effects model due to the presence of significant heterogeneity, $?^2_{df=27}=44.37$, $p<.019$.

The effect sizes for each domain were compared to the effect sizes estimated from practice effects (see Figure 1). The weighted effect sizes for Working Memory (95% CI=0.17-0.39), Verbal Fluency (95% CI=0.28-0.46), Motor Skills (95% CI=0.18-0.56), and Delayed Recall (95% CI=0.27-0.47) were significantly greater than the practice effects ESs.

Moderator Variables

Schizophrenia sub-type classification was not significantly associated with any cognitive domain nor was study duration significantly correlated with any domain effect size. The moderator variable control was significantly associated with both Verbal Fluency and Processing Speed indicating that studies that did not randomize subjects to treatments or were open label produced different effects sizes compared to those that included either of these features in their designs. Processing Speed effect sizes calculated from controlled studies were significantly smaller than those obtained from open label or non-random assignment studies, ES=0.26 vs. 0.47 ($Q_{BET}=5.44$, $p<.020$, $Q_W=44.89$, $p<.175$, $R^2=.11$). Recalculation of the weighted effect size for all SGAs indicated that the Processing Speed effect size remained significantly greater than zero

after excluding studies that did not randomly assign subjects to treatment or were open label (95% CI=0.15 – 0.37). Within medication group effect sizes decreased for clozapine, risperidone, and quetiapine (ESs=0.28, 0.19, and 0.24 respectively), and slightly increased for olanzapine (ES=0.56). The olanzapine and risperidone effect sizes remained significantly greater than zero after exclusion of the less controlled studies; however, the clozapine and quetiapine effect sizes did not.

In the case of Verbal Fluency, the weighted effect size for controlled studies was also significantly smaller than that observed in uncontrolled studies, ES=0.25 vs. 0.45 (Q_{BET}=4.13, p<.043, Q_W=30.30, p<.451, R^2=.12). The weighted effect size from controlled studies remained greater than zero though, (95% CI=0.13 – 0.37). Recalculation of within medication group effect sizes after excluding the uncontrolled studies indicated that the weighted effect sizes for clozapine, olanzapine, and risperidone decreased slightly (ESs=0.41, 0.23, and 0.04 respectively), and increased marginally for quetiapine (ES=0.68). The effect sizes for olanzapine, clozapine, and quetiapine still remained significantly greater than zero.

Comparison of Second Generation Medications

Pairwise comparisons between medication groups were carried out on each cognitive domain. Significant differences between medication groups were observed on the Vigilance (Q_{BET}=17.74, p<.0005, Q_W=26.63, p<.322, R^2=.40) and Verbal Fluency (Q_{BET}=14.41, p<.003, Q_W=20.03, p<.951, R^2=.42) domains. Follow-up contrasts within the Vigilance domain revealed a significant advantage for quetiapine, relative to clozapine ($?^2_{df=1}$=8.51, p=.004) and risperidone ($?^2_{df=1}$=13.10, p=.0003), and a significant advantage of olanzapine, relative to risperidone ($?^2_{df=1}$=7.97, p=.005).

Pairwise contrasts within the Verbal Fluency domain indicated that quetiapine improved performance to a greater extent than both risperidone ($?^2_{df=1}$=11.09, p=.0009) and olanzapine ($?^2_{df=1}$=4.30, p=.039) and clozapine improved performance to a greater extent than risperidone ($?^2_{df=1}$=9.19, p=.003). The pairwise contrasts were repeated after exclusion of the uncontrolled studies due to the fact that this moderator variable was associated with verbal fluency effect sizes. After excluding the less controlled studies, the quetiapine vs. risperidone and quetiapine vs. olanzapine contrasts remained significant ($?^2_{df=1}$=10.09, p=.0009 and $?^2_{df=1}$=4.30, p=.039) as did the clozapine vs. risperidone contrast ($?^2_{df=1}$=9.19, p=.003).

Within Group Effect Sizes

Clozapine was associated with significant improvements from baseline to endpoint on seven of the nine domains examined. These included improvements in Working Memory (ES=0.25), Learning (ES=0.31), Processing Speed (ES=0.35), Cognitive Flexibility and Abstraction (ES=0.25), Verbal Fluency (ES=0.44), Motor Skills (ES=0.64), and Delayed Recall (ES=0.25). After comparison to anticipated practice effect values, only the Verbal Fluency (95% CI=0.28-0.60) and Motor Skills (95% CI=0.29-0.99) domain effect sizes remained significant (see Figure 2).

Olanzapine also significantly improved performance in seven of the nine domains examined. These included improvements in the Vigilance (ES=0.45), Working Memory (ES=0.33), Learning (ES=0.43), Processing Speed (ES=0.57), Verbal Fluency (ES=0.28), Visuospatial Skill (ES=0.66), and Delayed Recall (ES=0.46) domains. The Processing Speed effect size was calculated under the random effects model, $?^2_{df=7}=16.75$, $p<.020$. When the practice effect values were used as a basis of comparison, only the Working Memory (95% CI=0.14-0.51) and Delayed Recall (95% CI=0.26-0.66) domains reached significance (see Figure 2).

Risperidone was associated with significant effect sizes in 5 of the 9 cognitive domains. These included significant improvements in Working Memory (ES=0.24), Learning (ES=0.39), Processing Speed (ES=0.30), Visuospatial Skill (ES=0.39), and Delayed Recall (ES=0.46). The Delayed Recall effect size (95% CI=0.26-0.46) was significantly greater than the practice effect size value (see Figure 2).

Within the Quetiapine group, significant improvements were observed in the Vigilance (ES=0.73), Processing Speed (ES=0.35), and Verbal Fluency (ES=0.63) domains. There was significant variability among the effect sizes that made up the weighted Delayed recall domain effect size, $?^2_{df=2}=6.51$, $p<.039$, therefore, the effect size for this domain was calculated under the random effects model. The improvements in Vigilance (95% CI=0.43-1.03) and Verbal Fluency (ES=0.36-0.90) were greater than that expected from practice alone (see Figure 2). The results for quetiapine should be interpreted cautiously given that the effect sizes for several domains included relatively few studies and, in the case of visuospatial skill, were based on a single study.

CHAPTER IV

DISCUSSION

The findings from the current set of meta-analyses indicate that SGAs improve performance in a number of cognitive domains. The results obtained from the current meta-analysis of 12 double blind, random assignment studies supported the findings of the earlier meta-analysis of five double blind studies that identified significant cognitive advantages with SGAs relative to FGAs. The greater number of studies included in the current meta-analysis of double blind, random assignment studies allowed for a finer delineation of the improvements and indicates that, relative to FGAs, SGAs improve performance on tests of learning and delayed recall, processing speed, and verbal fluency. More subtle benefits were also observed on aspects of working memory and motor skill. In general, there was not strong evidence that sample characteristics, such as treatment responsive vs. refractory or baseline medication status, had a prominent effect on cognitive change to SGA treatment in double-blind, random assignment studies. There was evidence that studies with a longer duration are associated with greater improvement on tests of cognitive flexibility and abstraction. There was also limited evidence that studies utilizing larger doses of haloperidol resulted in larger effect sizes with SGA treatment. Although correlations between haloperidol dose and effect size with SGA treatment was positively correlated with improvement in several domains, none reached statistical significance. Nonetheless, it is a noteworthy observation and suggests that some of the benefits observed with SGA treatments may, in part, relate to the larger doses of haloperidol used and associated blunting of cognitive performance.

The inclusion of investigations with single treatment arms and open label designs supported the benefits from SGA treatments reported in double blind, random assignment trials and extended the potential improvements to a wider array of neuropsychological tests. Indeed, every cognitive domain and virtually every neuropsychological test significantly improved with SGA treatment. The effect sizes for domains ranged from 0.18 to 0.37 and are remarkably consistent with Harvey & Keefe's (2001) review of 20 studies. For example, Harvey & Keefe's (2001) review identified improvements, in terms of Cohen's d, of 0.18 and 0.37 for executive functions and delayed recall respectively. The results reported here for cognitive flexibility and

abstraction and delayed recall were 0.18 and 0.39.

In contrast to prior reviews, the current meta-analysis carried out pairwise contrasts between SGAs in order to identify possible differences between treatments. No medication appeared superior or inferior to the other medications across all domains, but several differences emerged in two domains, Vigilance and Verbal Fluency. The results were generally consistent with predications derived from the assumption that lower dopamine activity and increased serotonin activity may be related to cognitive benefits from novel agents, but the results were not entirely consistent with the assumption that increased anticholinergic properties might limit gains in memory and attention. Risperidone, presumed to have the greatest activity at dopamine receptors (Seeman, 2002), showed the least beneficial profile on measures of vigilance and verbal fluency, being outperformed by quetiapine and olanzapine on vigilance, and quetiapine and clozapine on verbal fluency. The differences were quite robust and ranged from 0.3 to 0.5 standard deviations. Clozapine, presumed to have substantial inherent anticholinergic properties, did not significantly improve any test of vigilance and it resulted in less improvement than quetiapine on this domain. Moreover, although clozapine significantly improved delayed recall, these gains were significant on only one test, VLL II, and overall improvement in this domain was markedly less than that observed in the olanzapine and risperidone groups. However, despite the presumption of significant inherent anticholinergic activity, olanzapine did not conform to this model. Olanzapine led to medium to large gains on tests of vigilance and delayed recall. It thus appears that, at least at the dosages used here, olanzapine's anticholinergic effects may not be sufficient to impair memory or attention. These data tend to converge on the absence of central anticholinergic symptoms or cognitive impairment observed in patients with Alzhiemer's disease treated with very low doses of olanzapine (Kennedy et al., 2001; Street et al., 2000) and the lower incidence of cholinergic-related side effects and serum anticholiergic levels observed with olanzapine relative to clozapine (Eschweiler et al., 2002; Chengappa et al., 2000).

Analysis Two also examined the influence that moderator variables might have on effect sizes associated with SGA treatment. No widespread moderator effects were observed but a few test-specific effects were apparent. Studies that did not randomly assign subjects to treatment or were open label reported larger verbal fluency and processing speed effect sizes than studies that included either of these features in their design. Although the effects were modest and accounted

for a relatively small fraction of the variance, particularly in comparison to the differences between treatment groups, these observations are important and indicate that factors such as double blind and random assignment need to be considered when evaluating the literature on cognitive change to pharmacological treatments in schizophrenia. Overall, the results of the moderator variable analyses speak to the consistency of the results across different studies of SGAs suggesting that SGA benefit is not strongly influenced by schizophrenia sub-group classification, baseline medication status, or trial duration. Due to the small number of observations within each medication group, we were not able to fully explore the effect of moderator variables within each treatment group. This is unfortunate particularly in regard to duration of treatment, where longer trials of risperidone have failed to confirm the benefits from short duration trials, and where longer duration trials of olanzapine have produced greater benefit than shorter duration trials (Purdon et al., 2000; Green et al., 2002; Bilder et al., 2002; Harvey et al., 2003). In addition, the doses of SGAs used may also influence cognitive change. For example, larger doses of quetiapine have been associated with greater cognitive improvement (Velligan et al., 2002).

The moderator analysis is an effective method for detecting systematic variability between different studies of cognitive change to novel treatments, but it does not allow an assessment of more systematic challenges to the validity of the cognitive benefits reported from SGAs relative to FGAs or to the validity of differential benefits within the SGA class. The adjunctive use of anticholinergic medications and the failure to control for cognitive improvements that result from prior exposure to neuropsychological tests represent the two most problematic challenges to the validity of the SGA benefit. For example, although the double-blind design with random assignment to parallel treatment arms represents the gold standard for demonstrating differential efficacy, it is open to the confounding effects of a systematic differential utilization of adjunctive anticholinergic medications. In all studies with an FGA control arm, emergent extra-pyramidal symptoms will result in adjunctive treatment that will typically include an anticholinergic medication that will likely interfere with cognitive skills, particularly attention and memory. Although reports of differential efficacy from double-blind trials have occasionally included post-hoc analyses after stratification by anticholinergic use (e.g. Purdon et al., 2000), this is not the norm, and the relatively small sample sizes produced by stratification often renders the power of the study insufficient to detect an anticholinergic effect

on cognitive change.

A second systematic artifact relates to the possibility of practice effects that could occur on neuropsychological measures that are repeatedly administered to the same subject. In the double-blind studies, practice effects would be expected in both the SGA and the FGA treatment arms, and thus a relative advantage of SGAs would not likely be related to practice effects alone. However, this inference relies on the unsupported assumption that there will be no interaction between treatment and practice (Carpenter et al., 2002). To the contrary, emerging evidence suggests that first generation treatments may have a detrimental effect on new learning that may limit the benefit of repeated exposure to the same materials (Blyler & Gold, 2001). For example, a change to clozapine from FGAs resulted in improvement in procedural learning that may relate to a release from impairment caused by the FGA (Purdon et al., 2002), and intact procedural learning in unmedicated patients was compromised by 6 months' treatment with haloperidol but not olanzapine (Purdon et al., 2003). Similar demonstrations of a preservation of procedural learning with olanzapine and clozapine compared to the apparent loss of procedural learning induced by haloperidol, and perhaps risperidone, (Bedard et al., 1996; Bedard et al., 2000; Stevens et al., 2002) all tend to support the view that some of the improvements with SGAs might result from an avoidance of derogatory effects associated with FGAs rather than a novel enhancement of cognition. We undertook an exploratory examination of this hypothesis in Analysis Two by comparing the effect sizes derived from studies of SGAs with those calculated from longitudinal investigations of practice effects in schizophrenia patients and controls. After comparison to practice effects, the effect sizes for working memory, verbal fluency, motor skills, and delayed recall remained significant. Specifically, clozapine improved verbal fluency and motor skills, olanzapine improved working memory and delayed recall, quetiapine improved vigilance and verbal fluency, and risperidone improved delayed recall. Thus, it appears that although practice effects account for a significant portion of the cognitive improvements observed with SGAs, there are additional cognitive advantages with SGA treatments that exceed those expected from retesting alone. Our confidence in this finding must be tempered though by an appreciation of the limitations of the method used to establish the postulated practice effect magnitudes in the current investigation. Specifically, although longitudinal investigations of neuropsychological function in schizophrenia and controls do not report considerable differences in the degree of practice effects between groups and re-test intervals beyond three months do not

appreciably influence practice effects, the fact that the average practice effect values used here were based on test-retest intervals that were generally greater than 12 months in duration, whereas most cognitive change studies tend to be shorter, may have underestimated the true amount of improvement expected from practice (Heaton et al., 2001; Hoff et al., 1999; Censits et al., 1997; Dikmen et al., 1999; Basso, Bornstein, & Lang, 1999; Basso et al., 2001; Sweeney et al., 1991).

The improvements in cognitive performance with SGAs are in general encouraging, especially when the potential implications for socio-vocational re-integration are considered. The gains observed on tests of delayed verbal recall may be particularly relevant as this cognitive skill has been linked to three major dimensions of outcome including community/daily activities, social problem solving/instrumental skills, and psychosocial skill acquisition (Green, 1996; Green et al., 2000). Furthermore, the differential patterns of cognitive improvement combined with the knowledge that specific cognitive skills are linked to separate dimensions of outcome might also suggest that second generation treatments may be differentiated from one-another based on their unique effects on outcome. The strong gains observed in delayed recall with risperidone and olanzapine suggest that these treatments may be particularly effective at improving psychosocial skill acquisition. Furthermore, the robust improvements in vigilance observed with quetiapine, and to a lesser degree olanzapine, suggest that these treatments might have additional benefits to functional outcome. In contrast, clozapine's rather limited effects on delayed recall, but significant effects on verbal fluency, suggest that it may have a greater impact on community/daily living skills. Although direct evidence to test these predictions is limited, a recent double blind, random assignment study indicated that olanzapine improved quality of life based rating scales to a greater extent than risperidone (Gureje et al., 2003) and earlier investigations have indicated that olanzapine treated patients demonstrate greater improvement in work and social outcomes than haloperidol (Hamilton, Edgell, Revicki, & Breier, 2000). Pilot data from an earlier investigation also support the positive effects of olanzapine on functional outcome (Noordsy & O'Keefe, 1999). Similar improvements, relative to FGAs, in quality of life have also been reported for quetiapine (Velligan et al., 2003). Also, a recent 2 –year, random assignment study examining suicide attempts in patients receiving either clozapine or olanzapine indicated that clozapine is more effective at reducing suicide attempts and suicide related hospital admissions than olanzapine (Meltzer et al., 2003). One of the studies included in the

present analysis also examined functional outcome with clozapine treatment and although the outcome measure was restricted to discharge rates, the results are encouraging (Manschreck, Redmond, Candela, & Maher, 1999). Similar, data on reduced relapse rates have been reported for risperidone (Chengappa et al., 1999; Csernansky, Mahmoud, & Brenner, 2002).

The cognitive improvements to SGAs appear reliable, valid, and may be relevant to rehabilitation, but it is prudent to conclude this discussion with emphasis on the relatively small magnitude of the observed changes. Schizophrenia patients typically score more than a standard deviation below healthy controls on many of the neuropsychological tests reviewed here (Heinrichs et al., 1998). As a class, the SGAs improve all cognitive domains but the improvement is typically in the range of 0.20 to 0.40 standard deviations. These results are further attenuated when compared to anticipated practice related improvements. It is unlikely that the gains will be sufficient to return patients to the vocational level anticipated from their individual premorbid status. Indeed, improvements less than one standard deviation may not have any effect on outcome (Bellack, Gold, & Buchanan, 1999). However, the medication-specific effects of particular SGAs on particular cognitive domains could be relevant to the design of individual treatment plans that take into account the patient's premorbid intellect, unique profile of cognitive impairment, prior vocational achievements, and long term socio-vocational aspirations.

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Table 1. Neuropsychological Tests and Cognitive Domains	
	Abbreviation
Vigilance	
Continous Performance Test	CPT
Stroop Test (color-word score)	Stroop
Trailmaking A	TMA
Working Memory	
Verbal Working Memory	
Spatial Working Memory	
Learning	
Paragraph Recall\WMS-R Logical Memory (immediate)	LM I
Verbal List Learning tests (learning trials)	VLL I
Rey Design Learning Test	RDLT
Visual Reproduction	VR I
Cognitive Flexibility & Abstraction	
Wisconsin Card Sorting Test (pers. errors)	WCST
WAIS-R/III Similarities	SIM
Processing Speed	
Digit Symbol Substitution	DSST
Trailmaking B	TMB
WISC-R Maze Subtest	WISC Maze
Verbal Fleuncy (COWA & CIGT)	VF
Visuospatial Processing	
Block Design	BD
Complex Figure Test (copy)	CFT
Visual Organization	VOT
Motor Skills & Manual Dexterity	
Finger Tapping Test	FTT
Grooved Pegboard Test/PIN Test	GPB/PIN
Delayed Recall	
Paragraph Recall\WMS-R Logical Memory (delayed)	LM II
Verbal List Learning tests (delayed free recall)	VLL II
Visual Reproduction	VR II

ıble 2: Neuropsychological Change with Second Generation Treatment: Analysis 1.

		Number of Effect Sizes (k) and Number of Subjects (N)								Overall Weighted Effect Size					
		Clozapine		Olanzapine		Risperidone		Quetiapine							
		k	N	k	N	k	N	k	N	**k**	**N**	**ES**	**95% CI**	**Q Statistic**	**df**
GILANCE		**2**	**43**	**2**	**36**	**3**	**73**	**2**	**30**	**9**	**182**	**0.11**	**-0.09 - 0.32**	**2.52**	**8**
	Stroop	1	19	1	10	--	--	2	42	4	71	0.09	-0.26 - 0.44	0.55	3
	TMA	1	24	1	26	2	54	--	--	4	104	0.15	-0.12 - 0.43	1.59	3
	CPT	--	--	--	--	1	19	--	--	1	19	-0.07	--	--	--
ORKING MEMORY		1	24	2	46	4	87	1	11	**8**	**168**	**0.17**	**-0.05 - 0.39**	**2.49**	**7**
	Verbal Working Memory	1	24	2	46	4	87	1	11	8	168	0.09	-0.13 - 0.31	3.04	7
	Spatial Working Memory	--	--	1	20	2	39	1	11	4	70	0.39*	0.03 - 0.75	3.54	3
EARNING		**1**	**25**	**2**	**46**	**4**	**97**	**3**	**54**	**10**	**222**	**0.33***	**0.14 - 0.53**	**6.10**	**9**
	LM I	1	25	2	46	2	46	1	11	6	128	0.35*	0.10 - 0.61	2.48	5
	VLL I	1	24	2	46	4	97	3	54	10	221	0.32*	0.13 - 0.52	7.31	9
	VR I	1	24	2	46	2	46	1	11	6	127	0.48*	0.22 - 0.73	3.48	5
	RDLT	--	--	1	20	1	20	1	11	3	51	0.73*	0.30 - 1.15	0.65	2
ROCESSING SPEED		**2**	**42**	**3**	**56**	**4**	**93**	**3**	**54**	**12**	**245**	**0.27***	**0.09 - 0.46**	**9.53**	**11**
	DSST[b]	1	24	3	56	2	46	3	54	9	180	0.41*	0.08 - 0.74	17.36	9
	TMB	2	42	2	46	4	93	3	54	11	235	0.19*	0.00 - 0.38	4.89	10
OGNITIVE FLEXIBILITY & ABSTRACTION		**2**	**43**	**4**	**75**	**3**	**62**	**1**	**11**	**10**	**191**	**0.11**	**-0.10 - 0.32**	**7.48**	**9**
	SIM	--	--	2	30	1	20	1	11	4	61	0.29	-0.08 - 0.67	0.25	3
	WCST	2	43	4	75	3	62	1	11	10	191	0.10	-0.11 - 0.31	7.47	9
ERBAL FLUENCY		2	42	2	65	3	65	3	54	**11**	**226**	**0.26***	**0.06 - 0.45**	**7.89**	**10**
SUOSPATIAL SKILLS		**2**	**43**	**3**	**56**	**3**	**65**	**1**	**11**	**9**	**175**	**0.11**	**-0.10 - 0.34**	**8.38**	**8**
	BD	2	42	2	36	2	45	--	--	6	123	0.09	-0.16 - 0.35	8.53	5
	CFT	--	--	1	20	1	20	1	11	3	51	0.13	-0.28 - 0.55	4.59	2
	VOT	1	19	1	20	1	20	1	11	4	70	0.34	-0.13 - 0.69	2.63	3
OTOR SKILLS		**1**	**24**	**2**	**46**	**3**	**65**	**1**	**11**	**7**	**146**	**0.19**	**-0.05 - 0.43**	**7.08**	**6**
	FTT	1	24	2	46	2	46	1	11	6	127	0.30*	0.05 - 0.55	4.44	5
	GPB/PIN	--	--	1	20	2	39	1	11	4	70	0.15	-0.20 - 0.51	6.13	3
ELAYED RECALL		**2**	**43**	**1**	**26**	**2**	**50**	**2**	**43**	**7**	**170**	**0.24***	**0.02 - 0.46**	**3.00**	**6**
	LM II	2	43	1	26	1	26	2	43	6	138	0.06	-0.18 - 0.62	2.42	5
	VLL II	1	24	1	26	2	58	--	--	4	108	0.35*	0.08 - 0.62	2.35	3
	VR II	2	43	1	26	1	26	--	--	4	95	0.31*	0.02 - 0.60	1.08	3

Z-score > 1.96, p<.05.

Random effects model, chi-square p-value < .05.

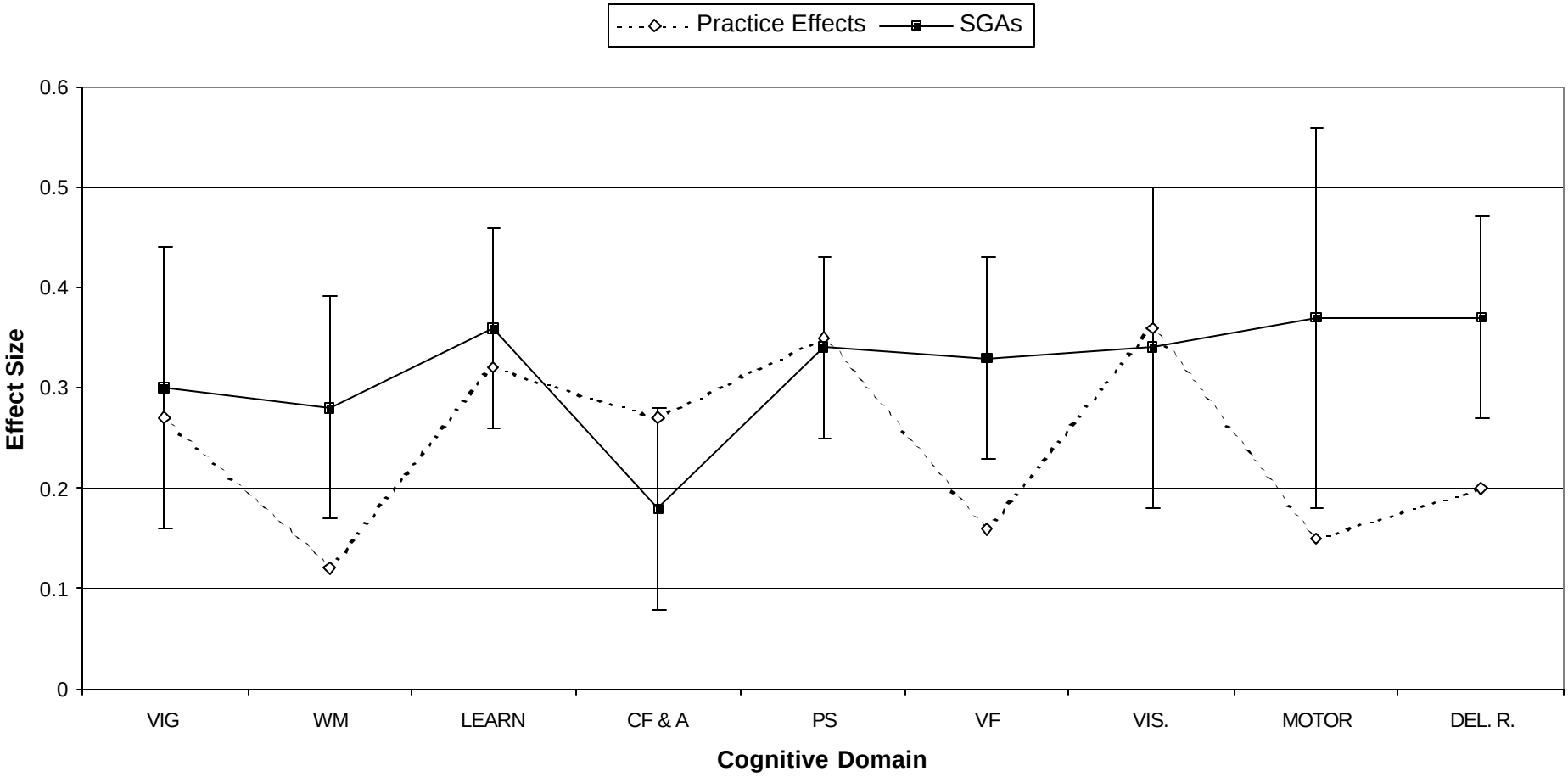
able 3: Neuropsychological Change with Second Generation Treatment: Analysis 2.

	Number of Effect Sizes (k), Number of Subjects (N), Mean Effect Size (ES)												Overall Weighted Effect Size		
	Clozapine			Olanzapine			Risperidone			Quetiapine					
	k	N	ES	k	N	ES	k	N	ES	k	N	ES	k	N	ES
GILANCE	**8**	**152**	**0.17**	**6**	**220**	**0.45***	**9**	**313**	**0.10**	**5**	**95**	**0.73***	**28**	**780**	**0.30*[a]**
Stroop	3	55	0.18	3	40	0.80*	2	43	0.15	3	58	0.67[a]	11	196	0.44*[a]
TMA	4	83	0.20	4	194	0.36*	4	241	0.07	2	93	0.23	14	557	0.19*
CPT	1	14	-0.08	2	149	0.46*	5	188	0.22	2	33	0.90*	10	384	0.35*
'ORKING MEMORY	**8**	**160**	**0.25***	**6**	**239**	**0.33***	**9**	**281**	**0.24***	**2**	**27**	**0.41**	**25**	**707**	**0.28***
Verbal Working Memory	8	160	0.24*	4	85	0.42*	8	156	0.25*	2	27	0.36	22	428	0.29*
Spatial Working Memory	1	18	0.46	5	213	0.34*	3	164	0.21	1	11	0.43	10	406	0.30*
EARNING	**10**	**221**	**0.31***	**6**	**203**	**0.43***	**7**	**225**	**0.39***	**6**	**112**	**0.24**	**29**	**750**	**0.36***
LM I	5	95	0.53*	3	62	0.43*	4	71	0.52*	1	11	0.90	12	239	0.51*
VLL I	10	209	0.26*	5	213	0.41*	6	239	0.39*	6	108	0.21	27	769	0.34*
VR I	5	98	0.27[a]	5	92	0.43*	3	58	0.32	2	34	0.16	15	282	0.32*
RDLT	--	--	--	1	20	0.41	1	20	0.25	1	11	0.75	3	51	0.42*
ROCESSING SPEED	**16**	**326**	**0.35***	**8**	**260**	**0.57*[a]**	**9**	**327**	**0.30***	**6**	**111**	**0.35***	**39**	**1024**	**0.34***
DSST	12	226	0.62*	6	102	0.68*[a]	5	96	0.53*	4	68	0.61*	27	492	0.61*[a]
TMB	12	241	0.19*	7	250	0.34*	7	290	0.23*	6	107	0.21	32	888	0.25*
OGNITIVE FLEXIBILITY & ABSTRACTION	**12**	**227**	**0.25***	**7**	**237**	**0.16**	**4**	**189**	**0.10**	**3**	**50**	**0.33**	**26**	**703**	**0.18***
SIM	4	68	1.31*	2	30	0.66*	1	20	0.26	1	11	1.38	8	129	0.72*
WCST	10	185	0.15	7	237	0.14	4	189	0.10	3	50	0.28	24	551	0.14*
ERBAL FLUENCY	**15**	**319**	**0.44***	**7**	**259**	**0.28***	**5**	**207**	**0.06**	**6**	**107**	**0.63***	**33**	**892**	**0.33***
SUOSPATIAL SKILLS	**9**	**179**	**0.20**	**4**	**66**	**0.66***	**3**	**65**	**0.39***	**1**	**11**	**0.56**	**17**	**321**	**0.34***
BD	8	164	0.26*	3	46	0.65*	2	45	0.58*	--	--	--	13	225	0.38*
CFT	1	22	0.23	2	30	0.52*	1	20	-0.30	1	11	0.52	5	83	0.24
VOT	4	87	0.03	1	20	0.77	1	20	0.25	1	11	0.60	7	138	0.21
OTOR SKILLS	**4**	**68**	**0.64***	**3**	**65**	**0.33**	**3**	**66**	**0.22**	**2**	**34**	**0.20**	**12**	**233**	**0.37***
FTT	4	68	0.64*	3	62	0.27	2	46	0.19	2	34	0.01	11	210	0.32*
GPB/PIN	--	--	--	1	20	0.66	2	39	0.14	2	34	0.39	5	93	0.34*
ELAYED RECALL	**13**	**280**	**0.25***	**4**	**199**	**0.46***	**5**	**211**	**0.46***	**3**	**58**	**0.30[a]**	**25**	**748**	**0.37***
LM II	6	108	0.35[a]	2	42	0.71*	3	51	0.53*	2	43	0.64*	13	244	0.49*
VLL II	8	173	0.29*	4	199	0.46*	3	186	0.70*[a]	1	15	-0.46	16	573	0.43*[a]
VR II	8	165	0.18	3	62	0.63*	2	38	0.80*	--	--	--	13	265	0.38*[a]

Effect Size > 0, p<.05.

Random effects model used to combine ESs, Chi-square p-value<.05.

Figure 1. Cognitive change with SGAs Compared to Practice Effects.



Abbreviations: VIG=Vigilance, WM=Working Memory, LEARN=Learning, CF & A=Cognitive Flexibility & Abstraction, PS=Processing Speed, VF=Verbal Fluency, VIS=Visuospatial Skills, MOTOR=Motor Sk ills, DEL. R.=Delayed Recall.

Figure 2. Cognitive change with clozapine, olanzapine, risperidone, and quetiapine: comparison to practice effects.