Psychopharm

Journal of Psychopharmacology
20(3) (2006) 335–346

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881105057002

The impact of atypical antipsychotic medications on long-term memory dysfunction in schizophrenia spectrum disorder: a quantitative review

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Abstract

This meta-analytic review examines the efficacy of antipsychotic medications in ameliorating schizophrenia-related long-term memory (LTM) impairments. Twenty-three studies were reviewed that compared schizophrenia spectrum patients treated (a) with atypical versus typical antipsychotic medications, or (b) with various atypical treatments. In 17 atypical versus typical trials aggregating 939 participants, superior overall (verbal and nonverbal) LTM was detected in patients assigned to atypical trials. However, this difference was small (effect size estimate (ES) 0.17; 95% Confidence Interval (CI) 0.04 to 0.31) and specific to certain atypical treatments. Relative to typical antipsychotic trials, LTM superiority was marginally significant for risperidone trials (ES 0.20; 95% CI −0.03 to 0.44) and significant for olanzapine trials (ES 0.29; 95% CI 0.08 to 0.49). In contrast, clozapine trials did not produce a LTM advantage over typical trials (ES −0.06; 95% CI −0.35 to 0.23). Due to the lack of available studies, the effect of quetiapine was indeterminate. Direct comparison between atypical trials revealed a similar effect pattern. A marginally significant superiority in overall LTM was detected for risperidone and olanzapine compared to clozapine (ES 0.28; 95% CI −0.04 to 0.59), which reached significance for verbal LTM (ES 0.36; 95% CI 0.04 to 0.67). Finally, the beneficial impact of antipsychotic medications emerged as a function of differences in the anticholinergic properties of the treatment arms being compared.

Keywords

schizophrenia, memory, cognition, atypical antipsychotic, pharmacotherapy, meta-analysis

Introduction

Second generation atypical antipsychotic medications are considered to preferentially improve cognition in schizophrenia in comparison to typical medications (Bilder *et al.,* 2002; Harvey and Keefe, 2001; Keefe *et al.,* 1999; Meltzer and McGurk, 1999). However, there is controversy as to how consequential these apparent benefits are. Carpenter and Gold (2002) recently proposed that the atypical medications may offer 'no efficacy' in *directly* promoting cognition. Rather, these medications may 'merely lack' the negative cognitive consequences inherent to first generation, typical medications (p. 969). This contention is based on the apparent adverse impact that typical medications have on motivation and motor and cognitive speed, as well as their association with increased use of anticholinergic medications. In light of this controversy the current quantitative review systematically evaluates studies investigating the differential impact of atypical and typical antipsychotic medications on long-term memory (LTM).

Despite the prominence of LTM dysfunction in schizophrenia (Aleman *et al.,* 1999; Heinrichs and Zakzanis 1998) the extent to which LTM is improved by atypical antipsychotic medications has not been systematically ascertained. While single-sample methodologies (e.g., Kern *et al.,* 1999; Velligan and Miller 1999) and pre-

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vious effect size analyses (Harvey and Keefe, 2001; Keefe *et al.,* 1999) provide preliminary indications of an atypical antipsychotic benefit in LTM, several noteworthy limitations in this research literature persist. Broadly, these limitations include the potential inaccuracy of the magnitude of LTM benefit derived from past integration of the research literature (Harvey and Keefe, 2001; Keefe *et al.,* 1999; Meltzer and McGurk, 1999) and a lack of specification of the conditions under which atypical medications effectively bolster LTM.

In terms of the former, while a prior effect size analysis suggests that atypical antipsychotic medications improves LTM moderately in comparison to typical medications (Harvey and Keefe, 2001), this conclusion was derived from an analysis that included studies that evaluated change in LTM from baseline assessment (i.e., switch studies). Unfortunately, such studies may have contaminated the atypical versus typical antipsychotic effect estimate with a practice effect involving carryover improvements at follow-up. This is particularly problematic in the serial assessment of LTM, since practice effects in this domain are among the largest (Lineweaver and Chelune, 2003).

Several limitations in the current literature are also apparent in our understanding of the conditions under which LTM benefits emerge. First, the extent to which the *individual* atypical medications differentially impact LTM has not been established. Consequently, the notion that LTM is enhanced by atypical medications in general may require qualification. Similarly, both pharmacological aspects of the treatments and research designs vary across the studies and may also moderate LTM outcomes. For example, determining whether differential LTM benefits are associated with randomized versus non-randomized designs is crucial in evaluating the significance of the apparent LTM benefits. Likewise, the underpinnings of LTM advantage may be illuminated if outcomes are moderated by factors such as the anticholinergic activity of the medications under comparison.

The current work utilizes a quantitative integration of past research to clarify the magnitude of LTM benefit associated with atypical medications and investigates the parameters associated with any benefit. If LTM benefits are robust, atypical medications may offer new opportunities to address an important source of dysfunction and loss in patients with schizophrenia. Such results would argue against Carpenter and Gold's (2002) notion that atypical medications offer no *direct* benefit in promoting cognition. Conversely, if improvements in LTM are trivial and/or accounted for by nonspecific secondary factors or research design artifacts then impairments would be less clinically and therapeutically relevant. This pattern of findings would parallel a prior quantitative integration of randomized symptom treatment trials showing that the enhanced efficacy and the tolerability of atypical medications was accounted for by trials involving higher than recommended dosages of the typical antipsychotic comparator (Geddes *et al.,* 2000).

Methods

Selection of studies

All studies selected for inclusion were English language publications that evaluated (1) the impact of atypical versus typical medications on the declarative (explicit) LTM of schizophrenic, schizoaffective or schizophreniform patients or (2) compared the LTM outcomes of different atypical medications in these patient groups. Studies were identified through a computerized search of *Medline*/*PubMed, EMBASE* and *PsychInfo* databases 1988 through 2003 (keywords available upon request), inspection of published reference entries from major review articles, and a 1988 through 2003 journal-by-journal search of *American Journal of Psychiatry*, *Biological Psychiatry*, *Schizophrenia Bulletin*, and *Schizophrenia Research*. Table 1 summarizes characteristics of the 23 studies identified.

LTM effect procedures

For our main analysis, the differential impact of atypical compared to typical medications was analysed at follow-up intervals occurring after an adequate drug trial had been achieved, but at points when attrition was minimal (range: 4–54 weeks; see Table 1). Distinct from the limited-capacity processing buffer comprising short-term and working memory, LTM involves a relatively permanent aspect of the memory store that allows retrieval of recently acquired information after distraction or delay (see Atkinson and Shiffrin, 1968; Butters and Delis, 1995). Long-term memory is further distinguished from remote memory, which involves memory for information consolidated years or decades earlier (e.g., Butters and Delis, 1995; Cohen and Squire, 1981). We operationally defined LTM as a permanent memory store that is invoked (1) when information can no longer be held in immediate awareness because of its quantity or (2) after a significant delay or distraction period. Long-term memory tasks encompass both verbal and nonverbal immediate and delayed recall (free and cued) and recognition for target materials. Table 2 documents the LTM tasks that were compiled to estimate effects from each study.

In terms of the LTM tasks targeted in this review, certain exclusion criteria were employed. Specifically, measures assessing the percentage of information retained after delay were excluded as these measures confound initial target material recollection with memory retention. Likewise, measures of recall pattern were excluded because these scores confound the amount of target material remembered with the pattern of memory performance. Finally, remote memory tasks were excluded because they do not meet established definitions of LTM.

In evaluating the LTM effects, preference was given to outcomes derived from between- rather than within-subject comparisons. The rationale for this choice is twofold. First, differences in baseline treatments may complicate interpretations of within-subject effects (Harvey and Keefe, 2001). Without a comparison group for evaluating differential between-group change, improvements from baseline may primarily reflect differences in the baseline conditions across the studies. Secondly, repeated LTM testing

Table 1 Design parameters for 23 included studies

Typical vs. atypical studies	Follow-up weeks	Treatment design	Setting	Neuroleptic responsiveness
Bilder *et al.*, 2002	12.5*	Randomized double blind	Inpatient	Resistant
Buchanan *et al.*, 1994	10*	Randomized double blind	Outpatient	Responsive
	52			
Cuesta *et al.*, 2001	13*	Non-random naturalistic	Outpatient	Partially responsive
	26			
Earnst *et al.*, 1999	Naturalistic	Non-random naturalistic	Inpatient	Not reported
Fennig *et al.*, 2002	26*	Non-random naturalistic	Outpatient	Responsive
Green *et al.*, 2002	4*	Randomized double blind	Outpatient	Not reported
	104			
	4*			
Kern *et al.*, 1999	Flexible phase	Randomized double blind	Inpatient	Resistant
Lee *et al.*, 1999	6*	Randomized open	Not reported	Responsive
	26			
	52			
Milas *et al.*, 1999	22*	Randomized double blind	Outpatient	Responsive
Potkin *et al.*, 2001	5.5*	Cross over double blind	Inpatient	Mixed
Purdon *et al.*, 2000	6*	Randomized double blind	Outpatient	Mixed
	30			
	54**			
Purdon *et al.*, 2001	8	Randomized double blind	Inpatient	Not reported
	26**			
Rollnik *et al.*, 2002	3	Non-random naturalistic	Inpatient	Not reported
	12*			
Rosenheck *et al.*, 2003	26*	Randomized double blind	Inpatient and outpatient	Resistant
	39			
	52			
Velligan *et al.*, 2002	24*	Randomized double blind	Outpatient	Responsive
Velligan *et al.*, 2003	13*	Randomized rater blind	Outpatient	Resistant
	26			
Weiser *et al.*, 2000	At least 4*	Non-random naturalistic	Inpatient and outpatient	Not reported
Atypical vs. atypical studies	Follow-up weeks	Treatment design	Setting	Neuroleptic responsiveness
Daniel *et al.*, 1996	6*	Cross-over single blind	Outpatient	Resistant
Harvey, *et al.*, 2003	8*	Randomized double blind	Inpatient and outpatient	Responsive
Harvey, *et al.*, 2003	8*	Randomized double blind	Inpatient and outpatient	Not reported
Lindenmayer *et al.*, 1998	12*	Non-random open	Inpatient	Resistant
Nieman *et al.*, 2002	6*	Randomized double blind	Inpatient and outpatient	Responsive
Sharma *et al.*, 2003	6*	Non-Random naturalistic	Not reported	Resistant
	26			

Notes: *Indicates the number of treatment weeks corresponding to the effects that were incorporated into the most inclusive analyses. **Indicates that effects were incorporated from a treatment reflecting the last observation carried forward.

Table 2 Long-term memory measures used in effect calculations

Typical vs. atypical	Verbal LTM	Nonverbal LTM	Composite LTM
Bilder *et al.*, 2002	WMS-R: verbal, immediate and delayed HVLT: total and delayed	WMS-R: visual, immediate and delayed	–
Buchanan *et al.*, 1994	WMS-R: verbal	WMS-R: visual	–
Cuesta *et al.*, 2001	WMS: verbal	WMS: visual Rey figure	–
Earnst *et al.*, 1999	WMS: Verbal	WMS: Visual	-
Fennig, *et al.*, 2002	Paired associates	Rey figure	Rivermead Behavioral Memory Test
Green *et al.*, 2002	CVLT: trials 1–5 recall and recognition	–	–
Kern *et al.*, 1999	CVLT: trials 1–5 recall and recognition	-	-
Lee, *et al.*, 1999	Verbal list learning: immediate and delayed recall	–	–
Milas, *et al.*, 1999	Benton serial digital learning Auditory verbal learning	–	–
Potkin *et al.*, 2001	WMS-R: verbal RAVLT: trial 5, delayed recall, delayed recognition	WMS-R: visual	–
Purdon *et al.*, 2000	Rey/Crawford Auditory Verbal Learning Test Story Recall Test	Rey Serial Design List Learning Test WMS: visual Rey figure: immediate	–
Purdon *et al.*, 2001	Rey/Crawford Auditory Verbal Learning Test Story Recall Test	Rey Serial Design List Learning Test WMS: visual Rey figure: immediate	–
Rollnik *et al.*, 2002	–	Benton Visual Retention Test	–
Rosenheck *et al.*, 2003	–	–	Factor-analytically derived memory score from test battery
Velligan *et al.*, 2002	HVLT: total Paragraph recall: 15 min delay	–	–
Velligan *et al.*, 2003	CVLT: trials 1–5	–	–
Weiser *et al.*, 2000	RAVLT: trial 5	–	–
Atypical vs. atypical	**Verbal LTM**	**Nonverbal LTM**	**Composite LTM**
Daniel *et al.*, 1996	WMS: verbal	WMS: visual Rey figure Facial recognition	–
Harvey *et al.*, 2003	CVLT: trials 1–5 recall, delayed recall, recognition	–	–
Harvey, *et al.*, 2003	Serial Verbal Learning Test: total, delayed		
Lindenmayer *et al.*, 1998	Paragraph Memory Test: verbatim and paraphrase HVLT: recall and recognition	Pattern Memory Test: recall and recognition	–
Nieman *et al.*, 2002	CVLT: trials 1–5 recall, immediate recall, delayed recall, recognition descrimination	Rey figure: delayed	–
Sharma *et al.*, 2003	WMS: verbal, immediate and delayed HVLT: immediate and delayed	WMS: visual, immediate and delayed	–

Notes: CVLT = California Verbal Learning Test; HSLT = Hopkins Serial Learning Test; HVLT = Hopkins Verbal Learning Test; RAVLT = Rey Auditory Verbal Learning Test; VLL = Verbal List Learning; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale Revised.

in within-subject comparisons (especially in uncontrolled 'switch' studies) are vulnerable to LTM practice effects (Harvey and Keefe 2001).

Effect size calculation and analysis

Sufficient information was either reported in the studies or made available upon request to permit effect calculation across two or more treatment arms. The effect size estimate used in the analysis, Cohen's *d* corrected for small-sample bias (Hedges and Olkin, 1985), was computed for each arm comparison as described below. This estimate is derived by subtracting the mean of one group (treatment arm) from that of the other group (treatment arm) and dividing by the pooled standard deviation of the groups. Subsequently, a weight is applied based upon sample size to correct for upward estimation of the effect in small samples. When means and standard deviations were not reported it was necessary to employ alternative techniques to derive effect estimates (Glass *et al.,* 1981). In order to maximize the inclusion of published reports in our analysis, two crossover design studies (Daniel *et al.,* 1996; Potkin *et al.,* 2001) were included by assuming that there was no effect for the order of treatments. In addition, for one study (Green *et al.,* 2002), effect sizes were estimated by assuming that the given median LTM performances were reasonable estimates of mean performances and by converting the reported semi-interquartile ranges into standard deviation units. Finally, because of the possibility of preexisting differences in LTM performance between treatment arms, whenever possible we removed baseline group differences by either subtracting differential LTM performance effects at baseline from the treatment follow-up effects or by calculating a between group effect based upon change from baseline scores (Lee *et al.,* 1999; Milas *et al.,* 1999).

All effects for studies comparing atypical and typical antipsychotic medications were coded so that a positive effect indicates LTM superiority for the atypically treated group. In supplemental atypical-atypical comparisons effects were coded as indicated in the notes of the relevant table. When multiple LTM measures were reported in a study, outcomes were pooled into a single effect for each task used in the study. Often this involved combining immediate and delayed measures of LTM from the same task. Thereafter, outcomes were combined into a single verbal and a single nonverbal effect for the study, and a combined effect was calculated as the arithmetic mean of the verbal and nonverbal effects. The exception to this was when the only data available was a composite score or when a study reported exclusively verbal or nonverbal outcomes (in which case the verbal or nonverbal outcome was taken as the overall effect). Finally, when a given study reported LTM outcomes for multiple atypical and/or typical medications, the data were pooled together to create a single LTM effect that was employed in the main analyses contrasting atypical to typical medications.

Using Hedges and Olkin's (1985) fixed effect model, as implemented in Comprehensive Meta-Analysis (Borenstein and Rothstein, 1999), *d*'s from each study were combined to provide an overall composite effect point estimate (ES) across the contributing comparisons. The estimate establishes the magnitude of the group difference in LTM between treatment arms. The corresponding 95% confidence interval (CI) reflects the precision of the estimate. To evaluate whether the samples had a common underling effect, the homogeneity of the estimates (i.e., *Q*-values) were calculated (Borenstein and Rothstein, 1999). When the overall *Q*-value is significant, homogeneity of the effect set is rejected.

Moderator analyses

While various characteristics of the effect sets were of interest as moderators, these characteristics often involved non-independent observations because the same subjects served in more than one comparison (e.g., for a given study the same subjects in the typical arm were compared to subjects in both the olanzapine arm and in the risperidone arm). Consequently, only the study design variable (see below), which maintains independence, was evaluated in the between-class analysis of homogeneity (i.e., Q_B; see Hedges and Olkin 1985). The Q_B statistic is analogous to an *F* statistic in testing class differences. In addition analyses, several continuous variables were tested as moderators by generating the appropriate correlation coefficient between the potential moderating variable and the set of effects.

Study design In order to evaluate whether study design moderated differences in LTM, effects were categorized based upon whether they were generated from randomized or cross-over designs versus nonrandomized trials. Note that the nonrandom studies were often non-blinded and naturalistic as well (see Table 1).

Anticholinergic load Differences in anticholinergic load between treatment arms may be an important moderating variable of the LTM effects. Antipsychotic medications vary in intrinsic anticholinergic properties, and in the likelihood of co-administration of adjunctive anticholinergic drugs. To evaluate the possible influence of anticholinergic activity on LTM, an anticholinergic load was calculated for each arm considered. Note that seven studies were excluded because it was not possible to obtain an accurate estimate of the antipsychotic medication dose for all treatment arms. Because antipsychotic medications exhibit differential activity at muscarinic receptors and differential inducement of anticholinergic side effects, the impact of anticholinergic load was determined for each arm separately, rather than pooling the LTM effects from the various arms.

The values for anticholinergic activity were taken from two published scales (Minzenberg *et al.,* 2004). The first of these ('pharmacological index') is based on the affinity of drugs for in vitro muscarinic receptor antagonism. As examples, on the pharmacological index 8 mg clozapine has an anticholinergic equivalency of 1 mg of benztropine; while haloperidol has essentially no anticholinergic activity on this scale. The second scale ('clinical index') is derived from expert clinicians' ratings of the likelihood of specific drugs to induce anticholinergic side effects. As examples, on the clinical index 85 mg clozapine and 13 mg haloperidol have an anticholinergic equivalency of 1 mg of benztropine (Minzenberg *et al.,* 2004).

In our calculations, anticholinergic estimations for each arm were based upon the mean anticholinergic load equivalent to 1 mg/day benztropine. The anticholinergic load comprised the sum of the intrinsic anticholinergic activity of the specific antipsychotic, as well as the activity associated with co-administration of adjunctive drugs. The calculations used dose as a multiplier. If the number or proportion of patients using adjunctive anticholinergic medications was reported for an arm, without reference to the doses employed, our estimates assumed that each patient treated with these adjunctive drugs received 1.5 mg/day benztropine (the middle of the recommended dose range; Bezchlibnyk-Butler and Jeffries, 1998).

To evaluate the anticholinergic influence on LTM, point estimates were reported based upon the magnitude of the anticholinergic discrepancy between the atypical and typical arms as determined by our implementation of the anticholinergic scales (Minzenberg *et al.,* 2004). For these estimates, each effect in the set of effects under consideration was categorized into one of two groups based upon the anticholinergic load discrepancy of the atypical compared to typical arm. Specifically, one group of effects was comprised of comparisons in which the between-arm differences in anticholinergic load fell below the median of the set; the second group of effects had differences that fell at or above the median. The LTM point estimates from the 'below-median groups and those from the 'above-median' groups were subsequently inspected. Note that the below-median effect group contains discrepancies that tend to be negative, indicating that the anticholinergic load of the atypical arm was generally greater than the typical arm (i.e., 'atypical shifted anticholinergic activity'). In contrast, the above-median effect group contains positively valued discrepancies, indicating that the constituent effects were based on comparisons in which the typical arms have greater anticholinergic load than the atypical arms (i.e., 'typical shifted anticholinergic activity').

To further investigate the relationship between anticholinergic load and LTM, additional point estimates were calculated by compiling both the atypical-typical and atypical-atypical effects. For these comparisons, we were interested in determining whether the absolute discrepancy in anticholinergic load between treatment arms moderated the magnitude of LTM effects. Therefore, effects were coded to specify the relative anticholinergic properties of the arms; positive effects indicate that the lower-load anticholinergic arm produced relatively superior LTM, while negative effects indicate that the higher-load anticholinergic arm produced relatively superior LTM. This anticholinergic-based LTM effect coding systematizes the direction of the effects (i.e., the effects' signs), permitting a direct evaluation of whether LTM estimates varied as a function of the absolute difference in anticholinergic load. Note that three effects were dropped from the pharmacological index analyses because there was no difference in the anticholinergic load between medications, and thus the LTM effect sign could not be assigned.

As in the atypical-typical anticholinergic analyses, point estimates were reported according to the magnitude of the anticholinergic discrepancy between treatment arms. Effects were again categorized based upon the median between-arm differences in anticholinergic load. However, in these comparisons the 'below-median' group was comprised of LTM effects with lower (nearer to the finite endpoint of zero) anticholinergic load discrepancies, while the 'above-median' group contained the higher anticholinergic discrepancies.

Typical neuroleptic dose based upon chlorpromazine (CPZ) equivalency To evaluate whether the dosage of typical medications moderates LTM, dosages for the typical medications were converted to a comparable daily dosage (CPZ equivalency) based on D_2 affinity (Bezchlibnyk-Butler and Jeffries 1998). Subsequent Pearson correlation coefficients were estimated between the CPZ equivalency and the effect estimates. Differential CPZ equivalency between typical and atypical arms were not analysed because of the difficulty in estimating blockade for atypical medications.

Clinical and demographic moderators A number of clinical and demographic variables were assessed as potential moderators of the difference in LTM performance between treatment arms. Psychiatric symptom severity at baseline was examined by assessing the correlation between coverall LTM outcomes and composite, positive and negative baseline symptom scores (e.g., PANSS Total, BPRS), as well as differences in these scores for patients assigned to atypical versus typical medications. Since several different symptom assessment scales were used across the included studies, we standardized the scales. This procedure involved dividing each sample's mean score by the product of the number of items and the highest possible value for each item on the scale (which required an adjustment for studies in which the minimum item score was 1 rather than 0), thereby producing a value for each study on a scale from 0 to 1, with 0 indicating that all subjects received the minimum score on every item on the scale and with 1 indicating that all subjects received the maximum score on every item on the scale. When multiple scales were reported in a given study, data from the PANSS was used to the exclusion of other scales.

Demographic variables analysed as moderators included gender, age and educational differences across the treatment arms. Finally, an analysis was conducted to determine whether duration of follow-up was associated with effect magnitude. In this evaluation multiple effects from studies reporting more than one follow-up interval were all included in the analysis.

Results

Overall differences in atypical versus typical medication

Seventeen studies were retrieved and their outcomes were submitted to an overall analysis of LTM following atypical versus typical antipsychotic treatment. Fig. 1 illustrates the small but statistically significant superiority of LTM in patients assigned to atypical arms over those assigned to typical arms (ES 0.17). Interestingly, as can be seen in this figure, none of the studies included in the analysis produced individual effects that were significantly different from zero (see lower bound of the 95% confidence intervals).

This argues against the possibility of a 'file drawer effect' due

Study	Effect	95% Confidence Lower	Upper	N1	N2	*p*-value
Bilder *et al*., 2002	0.25	−0.21	0.71	76	25	0.28
Buchanan *et al*., 1994	0.11	−0.55	0.77	19	19	0.74
Cuesta *et al*., 2001	−0.22	−1.13	0.69	30	6	0.62
Earnst *et al*., 1999	0.39	−0.53	1.31	19	7	0.37
Fennig *et al*., 2002	0.44	−0.56	0.93	35	33	0.07
Green *et al*., 2002	−0.18	−0.69	0.34	30	31	0.48
Kern *et al*., 1999	0.40	−0.11	0.90	32	32	0.11
Lee *et al*., 1999	−0.39	−0.91	0.14	33	27	0.13
Milas *et al*., 1999	0.27	−0.75	1.28	10	8	0.56
Potkin *et al*., 2001	0.15	−0.64	0.95	14	13	0.69
Purdon *et al*., 2000	0.23	−0.38	0.84	40	15	0.45
Purdon *et al*., 2001	0.15	−0.74	1.04	11	11	0.72
Rollnik *et al*., 2002	−0.44	−1.40	0.52	11	9	0.32
Rosenheck *et al*., 2003	0.26	−0.03	0.55	97	90	0.08
Velligan *et al*., 2003	0.14	−0.60	0.88	15	16	0.69
Velligan *et al*., 2002	0.40	−0.21	1.00	43	15	0.18
Weiser, 2000	0.26	−0.28	0.79	47	20	0.33
Combined (17 studies)	**0.17**	**0.04**	**0.31**	**562**	**377**	**0.01**

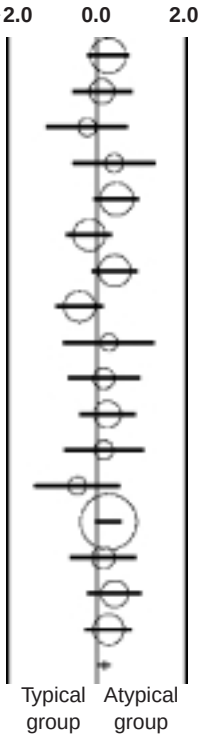

Figure 1 Long-term memory effect sizes of the primary studies comparing atypical and typical compounds

to under-representation of null results in the published literature. Table 3 (top panel) further decomposes the point estimate effects. The overall estimate remained reliable in studies randomizing patient assignment (ES 0.16), but the verbal and nonverbal estimates were not significant. Finally, no differences were found between the estimates derived from the 12 randomized/crossover designs versus the five non-randomized designs in overall, verbal, and nonverbal LTM (all $p > 0.5$).

LTM effects for atypical arms

In terms of the individual atypical treatments, Table 3 (middle panel) illustrates that relative to typical arms both olanzapine and risperidone are associated with superior overall and verbal LTM. In contrast, there is no apparent LTM advantage conferred by clozapine over typical arms. Additionally, while the 95% confidence interval of the quetiapine estimate overlapped with zero and consequently is not statistically significant, this analysis contained very few outcomes. Similarly, the number of nonverbal outcomes for all comparisons is very small.

Table 3 (lower panel) shows contrasts between the atypical arms themselves. While there was no differential LTM impact of risperidone relative to olanzapine, risperidone affords reliable verbal and overall LTM benefits over clozapine. The findings are inconclusive regarding the differential impact of olanzapine itself compared with clozapine, perhaps reflecting the few studies available for this analysis. The apparent trends favouring both risperidone and olanzapine over clozapine, is illustrated by combining the two former effect sets and then making a comparison to clozapine. These two arms taken together generate a verbal LTM estimate that is superior to that of clozapine. Quetiapine was not evaluated because no studies in our sample directly compared quetiapine to other atypical medications.

Moderation of LTM effects by pharmacological properties of the arms

Of substantial interest in the current review is the potential moderating impact of pharmacological aspects of treatment medications on LTM. Since multiple arms from several studies were used to generate effects, observations were non-independent; therefore, we limited the statistical treatment of this data. Nonetheless, relative differences between the anticholinergic loads of the arms appear to moderate the effect set.

The relationship between LTM effects and anticholinergic load is illustrated in Table 4 (top panel). By dichotomizing effects at the median value of the between-arm difference in anticholinergic load, statistically significant LTM benefits are reliably observed for atypical treatment arms that induce relatively lower anticholinergic load. These estimates are labelled ‘typically shifted

Table 3 LTM effect estimates for antipsychotic comparisons

Overall atypical-typical comparison	Outcomes	Cases	Point estimate (ES)	95% CI
Entire study set				
Overall	17	939	0.170**	0.04 to 0.31
Verbal	15	732	0.179**	0.02 to 0.33
Nonverbal	9	393	0.144	−0.07 to 0.36
Randomized studies				
Overall	12	722	0.159**	0.01 to 0.31
Verbal	11	535	0.119	−0.06 to 0.30
Nonverbal	5	393	0.196	−0.08 to 0.47
Individual atypical-typical comparison	**Outcomes**	**Cases**	**Point estimate (ES)**	**95% CI**
Clozapine versus typical				
Overall LTM	5	188	−0.064	−0.35 to 0.23
Verbal LTM	5	188	−0.062	−0.35 to 0.23
Nonverbal LTM	4	128	0.078	−0.27 to 0.43
Olanzapine versus typical				
Overall LTM	6	367	0.285**	0.08 to 0.49
Verbal LTM	5	180	0.310**	0.01 to 0.62
Nonverbal LTM	3	113	0.313	−0.08 to 0.71
Risperidone versus typical				
Overall LTM	7	295	0.203*	−0.03 to 0.44
Verbal LTM	7	295	0.255**	0.02 to 0.49
Nonverbal LTM	4	120	0.163	−0.21 to 0.53
Quetiapine versus typical				
Overall LTM	3	111	0.259	−0.15 to 0.66
Verbal LTM	3	111	0.232	−0.17 to 0.64
Nonverbal LTM	1	22	0.263	−0.63 to 1.16
Atypical medications comparison	**Outcomes**	**Cases**	**Point estimate (ES)**	**95% CI**
Risperidone versus Clozapine				
Overall LTM	4	118	0.318*	−0.05 to 0.69
Verbal LTM	4	118	0.491**	0.11 to 0.87
Nonverbal LTM	4	118	0.141	−0.22 to 0.51
Olanzapine versus Clozapine				
Overall LTM	2	80	0.260	−0.19 to 0.71
Verbal LTM	2	80	0.251	−0.19 to 0.70
Nonverbal LTM	2	80	0.265	−0.18 to 0.71
Olanzapine versus Risperidone				
Overall LTM	7	618	0.005	−0.15 to 0.16
Verbal LTM	7	618	−0.032	−0.19 to 0.13
Nonverbal LTM	4	158	0.115	−0.20 to 0.44
Olanzapine and Risperidone versus Clozapine				
Overall LTM	5	174	0.277*	−0.04 to 0.59
Verbal LTM	5	174	0.357**	0.04 to 0.67
Nonverbal LTM	5	174	0.174	−0.14 to 0.49

Notes: All homogeneity statistics (*Q*-values) were non-significant. For the atypical comparisons, positive values indicate superior memory for atypical medications listed on the left compared to those listed on the right. CI = confidence interval. * $p \leq 0.10$; ** $p \leq 0.05$.

anticholinergic activity'. In contrast, the point estimates are generally nonsignificant when relatively higher anticholinergic load is induced by the atypical arm (i.e., 'atypically shifted anticholinergic activity'). The relationship between anticholinergic load and LTM is further revealed when effects are systematically coded according to the arms anticholinergic load, rather than typicality versus atypicality. The lower panel of Table 4 illustrates that when there are higher between-arm anticholinergic load discrepancies the LTM point estimates (with positive values reflecting the LTM benefit of the lower anticholinergic arm) are almost universally reliable and relatively robust. In contrast, when arm discrepancies are minimal, the point estimates are very small and generally nonsignificant.

To determine whether typical neuroleptic dosage is associated with LTM, the CPZ equivalent dosages for the typical medications were correlated with the LTM effects. The findings from these analyses failed to reveal a significant relationship between overall LTM effects and CPZ equivalency (for overall, verbal and nonverbal LTM, all $ps > 0.5$). Nonetheless, higher CPZ equivalency was associated with the anticholinergic loads of the medications based on clinical ($r = 0.88$, $df = 12$, $p < 0.001$) and pharmacological ($r = 0.75$, $df = 12$, $p < 0.01$) scales.

LTM moderation based on clinical and demographic variables

To evaluate the clinical and demographic moderators of the LTM effects, we investigated the correlation of individual sample effects with duration of treatment, symptom severity indices, and basic demographic variables. None of these factors were significantly associated with overall LTM outcomes (all p-values > 0.17).

Discussion

The current quantitative review systematically evaluates the differential impact of atypical antipsychotic medications on LTM in persons with schizophrenia and identifies factors that moderate LTM outcomes. Our analyses of the extant LTM literature provide limited support for the contention that atypical medications offer LTM benefits over typical medications in the treatment of schizophrenia spectrum disorders. The observed benefit of atypical over typical medications, while reliable, is less than one fifth of a standard deviation. Based on this difference, the median LTM performance of patients treated with atypical medications would fall at approximately the 58 percentile of patient's treated with typical medications. By convention, this difference is considered to be small in magnitude (Cohen, 1988).

Using meta-analytic procedures, two prior reports of atypical-associated cognitive and memory change have been presented in the literature (Harvey and Keefe, 2001; Keefe *et al.,* 1999). In the earliest of these analyses, significance levels were combined across several cognitive domains. This approach provides no estimate of effect magnitudes, thus precluding comparisons with the current review. In a more recent review, Harvey and Keefe (2001) reported cognitive effects associated with atypical medication in schizophrenia. Their effect size for secondary memory (i.e., LTM) of approximately 0.4 was substantially larger than the present effect. However, the authors report aggregate LTM effects that represent either 'improvement from baseline in switch studies' or 'improvement relative to the conventional comparator in parallel studies' (p. 182). Test-retest 'switch' research designs are particularly vulnerable to the influence of practice when employing measures of LTM (Chelune *et al.,* 1993). For instance, in patients with schizophrenia LTM practice effect estimates from the first testing to a second testing (10 weeks) were modest at 0.52; and from the first testing to the third testing (14 weeks) were large at 0.81 (Hawkins and Wexler, 1999). Based on these LTM practice effects, it is likely that bias was introduced into Harvey and Keefe (2001) estimates that included switch studies. The current review was explicitly designed to minimize the bias arising from practice while simultaneously controlling for pre-existing differences in patients assigned to different arms. Thus, the current overall LTM estimate of 0.17 is likely to be an accurate estimate of the beneficial impact of atypical antipsychotic medication.

While the overall effect estimate is small, the current review also indicates that not all atypical medications are reliably associated with more positive LTM outcomes. Indeed, results suggest that while risperidone and olanzapine are associated with improved LTM, clozapine appears to confer no benefit over typical medications. Unfortunately, at this point in time the literature on quetiapine is inadequate to provide even preliminary impressions.

In a review of the cognitive outcome literature, Harvey and Keefe (2001) observed that the CPZ equivalency of the typical arms has been generally quite high. Subsequent research has suggested that low dose haloperidol has relatively comparable LTM benefits to those observed for risperidone and olanzapine (Green *et al.,* 2002; Keefe *et al.,* 2004). Consequently, it has been suggested that the neurocognitive advantage of atypical medications may occur only when the dosage of typical medications are high (Green *et al.,* 2002; Keefe *et al.,* 2004). In the current review this relationship is not revealed as we failed to detect an association between the LTM outcomes and dosage (CPZ equivalency) of the typical medications.

However, LTM is enhanced when treatment arms involve lower anticholinergic activity relative to comparator arms. Specifically, when there are higher anticholinergic activity discrepancies between treatment arms, LTM benefits emerge favouring the arm with the lower anticholinergic load. In contrast, when anticholinergic load is relatively equivalent between the arms, LTM is comparable. This was observed when point estimates based upon differential anticholinergic load were compiled from comparisons between both atypical-atypical and typical-atypical arms. Additional analyses also suggest that the specific LTM advantage of atypical over typical medications often discussed in the literature is most robust when typical arms have relatively higher anticholinergic activity.

The procedures used in the current research review captured both the inherent anticholinergic properties of the antipsychotic

Table 4 LTM as a function of the relative differences in anticholinergic load between treatment arms

Analysis set	Typical shifted anticholinergic activity				Atypical shifted anticholinergic activity			
Typical-atypical set	Discrepancy[a] range	Outcomes	Point estimate	95% CI	Discrepancy[a] range	Outcomes	Point estimate	95% CI
Overall LTM								
Clinical index	0.41 to 5.03	7	0.324*	0.10 to 0.55	−0.86 to 0.35	7	0.186	0.00 to 0.38
Pharmacological index	0.00 to 4.00	7	0.259*	0.05 to 0.47	−58.25 to −0.03	7	0.233*	0.04 to 0.43
Verbal LTM								
Clinical index	0.41 to 5.03	7	0.336*	0.11 to 0.56	−0.86 to 0.35	6	0.093	−0.16 to 0.35
Pharmacological index	0.00 to 4.00	7	0.274*	0.06 to 0.49	−58.25 to −0.03	6	0.165	−0.10 to 0.43
Nonverbal LTM								
Clinical index	1.04 to 5.03	4	0.384*	0.08 to 0.69	−0.86 to 0.63	3	0.110	−0.28 to 0.50
Pharmacological index	0.23 to 4.00	4	0.356*	0.05 to 0.66	−58.25 to −0.64	3	0.162	−0.22 to 0.54
	High anticholinergic load discrepancy				Low anticholinergic load discrepancy			
Anticholinergic set[b]	Discrepancy[c] range	Outcomes	Point estimate	95% CI	Discrepancy[c] range	Outcomes	Point estimate	95% CI
Overall LTM								
Clinical index	0.61 to 5.33	13	0.304**	0.13 to 0.48	0.13 to 0.56	13	0.080	−0.04 to 0.20
Pharmacological index	0.88 to 64.68	12	0.237*	0.06 to 0.42	0.03 to 0.87	11	−0.105	−0.24 to 0.03
Verbal LTM								
Clinical index	0.61 to 5.33	13	0.355**	0.18 to 0.53	0.13 to 0.56	12	0.063	−0.07 to 0.20
Pharmacological index*	1.34 to 64.68	11	0.333**	0.14 to 0.52	0.03 to 0.88	11	−0.035	−0.18 to 0.11
Nonverbal LTM								
Clinical index	1.05 to 5.33	8	0.300*	0.08 to 0.52	0.20 to 1.04	8	0.015	−0.22 to 0.25
Pharmacological index	4.00 to 64.68	8	0.157	−0.07 to 0.38	0.20 to 2.24	8	0.036	−0.19 to 0.27

[a]Negative discrepancy values indicate that the anticholinergic load of the atypical arm was greater than the typical arm. In contrast, positive values indicate that the anticholinergic load of the typical arm was greater than the atypical arms.

[b]LTM effects calculated so that the arm with the higher anticholingeric load was subtracted from the arm with the lower load.

[c]For these ranges the anticholinergic load discrepancy has a finite lower limit of zero, indicating no anticholinergic discrepancy between arms.

* $p \leq 0.05$, ** $p \leq 0.001$.

medications as well as the anticholinergic load conferred by adjunctive treatments. Virtually all studies that have addressed the impact of anticholinergic activity have evaluated the activity conveyed by the adjunctive medications alone without considering the anticholinergic properties of study medications themselves. The role of differential anticholinergic load and LTM modulation in schizophrenia likely reflects the well-established role of the cholinergic system in LTM functioning (Gold, 2003; Thiel, 2003). Prior single-sample research demonstrates that treatments involving higher anticholinergic activity result in inferior LTM in schizophrenia (Brebion *et al.,* 2004; Minzenberg *et al.,* 2004; Sweeney *et al.,* 1991). Our results replicate these findings within the context of antipsychotic medication trials and provide an explanation for the nature of differential LTM outcomes.

When the between-arm anticholinergic moderator is applied to the atypical versus typical effects, it is apparent that it accounts for a considerable amount of variability in outcomes. This observation can be viewed as being consistent with Carpenter and Gold's (2002) contention that atypical medications fail to directly promote cognition, but do so through secondary means. Nonetheless, our review suggests that to the extent that patients undergoing antipsychotic treatment can be managed in a manner that minimizes anticholinergic load, LTM may be supported. Furthermore, clinicians should be aware of the anticholinergic properties of all treatment medications when managing the memory impaired patient.

A specific limitation in the current review is that the number of studies available is relatively small; nonetheless, the integration of this research provides the most systematic review of this contentious literature to date. An additional concern is that the estimates of anticholinergic load may be prone to error. The procedures employed may underestimate the differential anticholinergic activity in select studies where specific adjunctive treatment data was not reported. Such reporting omissions in the literature would likely result in a systematic underestimation of the magnitude of typical versus atypical load difference. Despite this limitation, greater typical anticholinergic load was associated with a LTM advantage for atypical arms. Consequently, downward bias in anticholinergic load estimates would be unlikely to produce the observed associations between differential anticholinergic load and LTM.

Finally, we examined only LTM in the current study; consequently, the generalizability of the current set of findings to other aspects of cognition is unknown. Nonetheless, LTM is one of the most relevant cognitive domains to inspect. It is a prominent cognitive impairment in schizophrenia that has been associated with the daily functional abilities of afflicted patients (Aleman *et al.,* 1999; Green, 1996; Green, 2000; Heinrichs and Zakzanis, 1998). Additionally, on practical grounds, the literature on cognitive outcome following atypical medications is most voluminous in the area of LTM. Thus, evaluating LTM allowed us to inspect a relatively homogenous and well-established component of memory that can be assessed across several studies. Finally, the choice to review LTM was motivated by the specific methodological issues regarding LTM practice effects that were not accounted for in Harvey and Keefe's (2001) prior effect estimate.

In summary, the small atypical-related LTM advantage that we detected in the current review may, to a large extent, be conferred by differential anticholinergic properties of the treatment arms themselves. For instance, clozapine, the atypical medication with the largest anticholinergic load did not produce LTM benefits over typical medications. Furthermore, while our overall findings provide some direction in management of the LTM impairments in schizophrenia, the expectation that LTM dysfunction can be markedly reduced by atypical medications appears overly optimistic.

Acknowledgement

Portions of this work were presented at the 2003 International Congress on Schizophrenia Research, Colorado Springs, CO, USA. The authors wish to acknowledge Debbie Thomson for consultation on pharmacological aspects of this work and Wendy Loken Thornton for her comments on an earlier version of this manuscript. We also thank many of the authors of single-sample studies who generously provided additional data and information to assist in the statistical portions of this paper. AET and WGH were supported by a New Emerging Team Grant from the Canadian Institute of Health Research.

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