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A meta-analysis of cognitive change with haloperidol in clinical trials of atypical antipsychotics: Dose effects and comparison to practice effects

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Abstract

Prospective, double-blind, randomized trials comparing atypical antipsychotic drugs (APDs) to typical APDs, such as haloperidol, indicate that atypical APDs provide a modest benefit to cognitive function in schizophrenia. However, the validity of this inference has been contested by suggestions that the cognitive improvements observed with atypical APDs reflect practice effects associated with repeated testing on the same neuropsychological instruments, or an avoidance of a deleterious effect of haloperidol on cognitive function that might be dose related. These alternate hypotheses were assessed by meta-analyses that 1) examined the relationship between cognitive change and dose of haloperidol within the control arms of prospective atypical vs. typical APD clinical trials; and 2) compared the magnitude of change observed within the haloperidol arms of these studies to estimated practice effects for several commonly used neuropsychological measures. The results indicate that overall cognitive performance improves while on haloperidol. Studies that used a low dose of haloperidol (<10 mg) did not yield larger effect sizes for overall cognitive function or specific neuropsychological measures than studies that used a high dose (>10 mg), although doses greater than 24 mg appear to have deleterious effects. For two of the six neuropsychological tests examined (digit symbol substitution and verbal fluency) the magnitude of change observed was significantly less than practice effects. The results indicate that although haloperidol may cause deleterious effects at very high doses, or in specific cognitive domains, these effects are not likely to explain the broader range of cognitive improvements observed with atypical APDs.

Keywords: Schizophrenia; Neuropsychology; Haloperidol; Practice effects; Meta-analysis

1. Introduction

Cognitive impairment is common in schizophrenia and is recognized as an important determinant of functional outcome (Green et al., 2000; Green, 1996; Heinrichs and Zakzanis, 1998). Findings from numerous double-blind, random assignment clinical trials indicate that atypical antipsychotic drugs (APDs) such as clozapine, olanzapine, risperidone, and quetiapine, improve cognitive function, compared to typical APDs such as haloperidol, in schizophrenia (Bilder et al., 2002; Purdon et al., 2001, 2000; Lee et al., 1999; Harvey et al., 2003; Keefe et al., 2004). The improvements are observed in

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global cognitive function and in specific cognitive domains such as learning and processing speed; although the mean difference between atypical and typical APDs tends to be rather small with effect sizes ranging from 0.2 to 0.4 (Woodward et al., 2005). The benefits to cognition associated with atypical APDs are often attributed to the novel pharmacological actions of these agents which include, but are not limited to, their ability to enhance dopamine and acetylcholine release in the prefrontal cortex (PFC) (Ichikawa et al., 2002; Meltzer, 2004; Meltzer and McGurk, 1999).

In prospective atypical vs. typical APD trials in which patients undergo neuropsychological evaluation at baseline and again at least once after random assignment to treatment, any differences between treatments in the degree of change observed over time are attributed to an enhancement of cognition with atypical APDs and not the effect of repeated exposure to the neuropsychological test materials and/or assessment environment (i.e. practice effects) (McCaffrey et al., 2000). However, this conclusion relies on the assumption that haloperidol and associated increased use of adjunctive anticholinergic medications to control emergent extra-pyramidal symptoms (EPS) have benign cognitive profiles that do not interfere with normal cognitive processes, including practice effects. This assumption has been challenged by speculation that the cognitive benefits associated with atypical APDs may, in part, result from an avoidance of the deleterious effects associated with typical APDs rather than a novel enhancement of cognition (Carpenter and Gold, 2002; Tandon et al., 1999; Blyler and Gold, 2000; Kasper and Resinger, 2003; Purdon et al., 2003; Harvey and Keefe, 2001). Specifically, it has been argued that typical APDs, haloperidol in particular, may exert a subtle negative effect on cognition that impedes normal practice effects (Harvey and Keefe, 2001; Carpenter and Gold, 2002). Moreover, if the negative effect of haloperidol is dose related, then the relatively high doses of haloperidol used in some demonstrations of atypical APD cognitive advantages may have further biased the results (Carpenter and Gold, 2002; Geddes et al., 2000; Harvey and Keefe, 2001; Gold, 2004). In the context of corporate-sponsored clinical trails designed to determine the efficacy of atypical APDs, this may lead to inappropriate dosing of haloperidol in the control arm and a misattribution of the avoidance of a deleterious effect of high doses of haloperidol to a novel effect of the atypical APD under investigation.

Unfortunately, evidence to support or refute these alternate hypotheses remains sparse or largely circumstantial (Meltzer and Sumiyoshi, 2003). The hypothesis that typical APDs, primarily haloperidol, interfere with practice effects is reasonable given that haloperidol can elicit significant EPS and may also result in selective impairments in processing speed, motor skill, and procedural learning as a consequence of D2 receptor blockade in the dorsal striatum (Legangneux et al., 2000; Ramaekers et al., 1999; Kapur et al., 2000; Purdon et al., 2003, 2002; Bedard et al., 2000, 1996; Kumari et al., 1997). Anticholinergic medications used to treat EPS, which are typically prescribed with greater frequency in typical APD control arms of clinical trials, can also impair cognitive processes related to learning and memory (Zachariah et al., 2002; McGurk et al., 2004; Gelenberg et al., 1989; Spohn and Strauss, 1989). Interestingly, a recent meta-analysis of both longitudinal and cross-sectional studies found that, contrary to expectations, typical APDs actually improve overall cognitive function in schizophrenia compared to no treatment or placebo (Mishara and Goldberg, 2004). Although the previous meta-analysis of cognitive change to typical APDs did not find a relationship between dose or concealment of study drug and change in overall cognitive function, the extent to which the findings from the Mishara and Goldberg (2004) meta-analysis extend to double-blind, random assignment, atypical vs. typical APD clinical trials is uncertain given that more than half of the 34 studies included in the meta-analysis were naturalistic single sample, open label studies. In our previous meta-analysis of atypical APDs, we observed that the open label trials produced larger effect sizes for some neuropsychological domains indicating that results from open label trials do not always generalize to double-blind and/or random assignment trials. It must also be noted that in the Mishara and Goldberg meta-analysis only slightly more than a third of the studies examined cognitive change with haloperidol exclusively, leading to a potential confounding of effects between haloperidol and other typical APDs. Moreover, only one clinical trial comparing an atypical to a typical APD was included. This is an important qualifier in that clinical trials comparing atypical to typical APDs may suffer from unique biases such as a possible tendency towards using higher doses of haloperidol, prophylactic anticholinergic treatment, and corporate sponsorship which are unlikely to impact studies examining the effect of various typical APDs on cognition relative to placebo, or unmedicated patient groups. Finally, the previous meta-analysis by Mishara and Goldberg (2004) did not examine potentially selective deleterious effects of high doses of typical APDs on specific neuropsychological tests or cognitive domains such as processing speed and motor skill that, putatively, may be adversely affected by haloperidol.

The proposition that atypical cognitive efficacy trials are biased towards identifying positive effects because they utilized haloperidol doses that were too high was initially based primarily on the findings of a small study of risperidone vs. low dose haloperidol that failed to confirm the cognitive benefits of risperidone identified in earlier, largely corporate sponsored clinical trials that used higher doses of haloperidol (Green et al., 2002). Subsequent trials using lower doses of haloperidol and larger sample sizes confirmed the benefits of risperidone and other atypical APDs to overall cognitive function; although the differences tend to be smaller than earlier studies (Keefe et al., 2006; Harvey et al., 2005). Nonetheless, the relatively modest benefits of olanzapine and risperidone to cognition, compared to earlier trials, reported for two recent trials was attributed largely to the low doses of haloperidol used relative to earlier trials (Keefe et al., 2004, 2006). However, speculation that haloperidol has a subtle deleterious effect on cognition that interferes with normal practice effects in atypical APD clinical trials has relied on anecdotal reports without empirical substance (Meltzer and Sumiyoshi, 2003). To the contrary, slight improvement in cognition has been observed with haloperidol in several clinical trials (Purdon et al., 2000; Keefe et al., 2004), although the improvements have not been systematically examined and compared across clinical trials. Also, since placebo trials are understandably rare, there has been no estimation of the magnitude of the expected practice effects that haloperidol is deemed to modulate. The meta-analyses described below constitute a systematic quantitative review of the literature pertaining to haloperidol effects on cognitive skill reported from clinical trials of atypical APDs. The analyses will evaluate the hypotheses that haloperidol offers no cognitive benefit, that high dose haloperidol confers less improvement or even detriments to cognitive skill that are not apparent with low dose haloperidol, and that benefits observed with haloperidol will not equal the benefits anticipated from practice effects alone.

2. Methods

Prospective investigations of atypical APD efficacy were reviewed to extract the magnitude of the cognitive changes reported in haloperidol arms. The potential contribution of haloperidol dose was examined by stratification and comparison of low dose to high dose studies, and by analysis of correlations between haloperidol dose and the magnitude of the cognitive changes. The potential mitigation of practice effects from haloperidol was examined by comparison of the change observed in the haloperidol arms to practice effects estimated from healthy control samples.

2.1. Analysis one: cognitive change with haloperidol

2.1.1. Literature search, inclusion criteria, and coding of study characteristics

The literature search, inclusion criteria, and coding of study characteristics are identical to those used in our prior meta-analysis of cognitive change with atypical APDs (Woodward et al., 2005). However, the database of controlled studies used in the prior report was updated to include studies published or 'in press' as of July 2005 to capture two new large scale, double-blind random assignment studies comparing olanzapine and risperidone to haloperidol (Keefe et al., 2006; Harvey et al., 2005). Sixteen studies reporting data from fourteen independent clinical trials of atypical APDs met criteria for inclusion and are listed in Table 1. One study, Lee et al. (1999), randomized subjects to a variety of typical APDs, not exclusively haloperidol; however, this study was still included in the meta-analysis since haloperidol was the most common typical APD subjects received. Two studies included in the prior meta-analysis were excluded from this analysis (Smith et al., 2001; Velligan et al., 2003). One study, Smith et al. (2001), was not included because within group means and SDs for cognitive measures were not reported at the end of the double-blind phase of the trial, could not be derived from the reported statistics, and could not be obtained from the author. The second study, Velligan et al.

Table 1
Haloperidol studies included in meta-analysis

Study	Re-test interval
Bilder et al. (2002)	14
Buchanan et al. (1994)	10
Green et al. (2002)	4
Green et al. (1997)[a]	4
Harvey et al. (2005)	12
Keefe et al. (2004)	12
Keefe et al. (2006)	8
Kern et al. (1999)[a]	4
Lee et al. (1999)	6
McGurk et al. (1997)[a]	4
Liu et al. (2000)	12
Potkin et al. (2001)	5.5
Purdon et al. (2000)	6
Purdon et al. (2001)	24[b]
Rosenheck et al. (2003)	52[b]
Velligan et al. (2002)	24

[a] Studies reported data from same clinical trial.
[b] Endpoint data used instead of first retest.

(2003), was not included because test–retest means for cognitive measures were not reported or could not be derived from the reported statistics, and also because it was unclear how many subjects were randomized to continue receiving haloperidol during the trial. Studies were coded for author and year of publication, number of follow-up cognitive assessments and test–retest intervals, use of alternate forms for tests of learning and memory, mean or median dose of haloperidol, and the mean age, education, IQ, illness duration, and age at onset of patients included in the haloperidol group.

2.1.2. Neuropsychological tests and calculation of effect sizes

Effect sizes were calculated for overall cognitive function by calculating a Global Cognitive Index and selected neuropsychological tests in order to examine widespread and selective effects of haloperidol on cognition, respectively. Several studies reported a standardized cognitive summary score and in these cases the change in this score was used as the effect size for the Global Cognitive Index. For studies that did not report a standardized cognitive summary score, the Global Cognitive Index was calculated by averaging effect sizes across all neuropsychological tests included in the study. Mean effect sizes were also calculated for the specific neuropsychological tests listed in Table 2. In two cases, verbal list learning and Digit Symbol Substitution, highly similar tests were combined into a single measure. The choice of specific tests to include in this review was based on their frequency of use in clinical trials (the test was used in at least four studies comprising a total of at least 100 subjects), putative sensitivity to potentially deleterious effect of haloperidol (i.e. processing speed and motor skill), their established relevance to functional outcome in schizophrenia, and their correspondence with candidate tests for inclusion in the MATRICS cognitive battery (Green et al., 2000; Green, 1996; Nuechterlein et al., 2004).

The standardized mean difference (SMD) method was used to calculate effect sizes. Effect sizes were calculated within groups by subtracting the baseline score from the retest score and dividing the difference by the pooled baseline and retest standard deviations (SDs) (Dunlop et al., 1996). If baseline and retest means and SDs were not reported, then the effect size was estimated from the mean change score divided by its SD, if available, or from the t or F statistics when change scores were also not reported (Shadish and Haddock, 1994). For studies that included more than one follow-up assessment, only data from the first retest was used whenever possible in order to maximize the sample size from each study, and guard against a selection bias anticipated from a more frequent and early withdrawal

Table 2
Neuropsychological tests included in meta-analysis

Domain	Test	Abbreviation	Dependent variable
Attention			
	Trailmaking A	TMA	Time to complete
	Continuous performance test	CPT	d-prime
Processing speed			
	Digit symbol/modalities test	DSST	Number of items completed in time limit
	Trailmaking B	TMB	Time to complete
Executive function			
	Wisconsin Card Sorting Test	WCST	Perseverative or % perseverative errors
Verbal learning			
	California/Rey/Crawford/Bushcke/Verbal Learning Tests	VLLi	Total number of words recalled over learning trials
Delayed verbal recall			
	California/Rey/Crawford/Bushcke Verbal Learning Tests	VLLd	Number of words recalled from list after delay period
Verbal fluency			
	Controlled Oral Word Association Test	COWA	Number of words generated
	Category Instance Generation Test	CIGT	Number of words generated
Motor skill			
	Finger Tapping/Oscillation Test	FTT	Number of taps-averaged across both hands
	Grooved Pegboard Test	GPB	Time to complete-averaged across both hands

of patients assigned to haloperidol arms. Fourteen studies included only one re-test or reported data from the first re-test that could be used to calculate effect sizes [data were provided upon request from study authors for two trials (Keefe et al., 2006; Purdon et al., 2000)]. Trial endpoint data were used to calculate effect sizes for the remaining two studies (see Table 1). It is unlikely that these two trials produced exaggerated effect sizes given that the LOCF data used to calculate effect sizes for one, Purdon et al. (2001), was based on a total of 11 subjects, of which only 3 completed a third and final assessment, and inspection of the figures included in the original report of the other study, Rosenheck et al. (2003), indicated that patients within the haloperidol arm did not demonstrate any additional changes in cognition beyond the first re-test.

A weighted average effect size and 95% confidence interval (CI) was then calculated for the Global Cognitive Index and the selected neuropsychological tests by combining effect sizes across studies according to the fixed effects model (Hedges and Vevea, 1998). The fixed effects model was used because we were interested in drawing conclusions about the specific set of published atypical vs. typical APD clinical trials, not the more general issue of cognitive change with typical APDs. To assess the degree of variance in effect sizes across studies, a measure of effect size heterogeneity, the Q statistic, was also calculated for each neuropsychological test (Hedges, 1994). The critical alpha for the Q statistic was set at .10 (Petitti, 2001). When the assumption of homogeneity was rejected the effect sizes were combined using the random effects model (Hedges and Vevea, 1998). The weighted mean effect size, 95% CI, along with the total number of studies and subjects at follow-up for each neuropsychological test are reported. In addition, publication bias, the tendency for studies reporting significant effects to be more likely published than studies that did not find significant effects, was assessed by plotting Global Cognitive Index effect sizes against sample size (i.e. Funnel Plot). An absence of publication bias is usually assumed if the shape of the plot approximates the shape of a inverted funnel with greater spread of effect sizes around the mean for studies with smaller sample sizes than those with larger sample sizes (Begg, 1994).

2.1.3. Haloperidol dose and moderator variable analysis

Two methods were employed to examine potential associations between haloperidol dose and the magnitude of cognitive change observed. First, studies were divided into two groups, those that used a low dose of haloperidol (<10 mg) and those that used a higher dose (>10 mg), and compared on the Global Cognitive Index and each neuropsychological test. A cutoff of 10 mg was used because a recent dose response review of haloperidol in clinical trials indicated that 10 mg is the upper boundary of the maximal effective dose of haloperidol (Davis and Chen, 2004). Comparisons between studies were carried out by partitioning the overall Q statistic into a between (Q_{BET}) and within (Q_W) groups component (Hedges, 1994). A categorical moderator variable was considered significant if Q_{BET} was significant (critical alpha=.05). Second, correlations between haloperidol dose and effect sizes were carried out for the Global Cognitive Index and each neuropsychological test. Two studies (Potkin et al., 2001; Liu et al., 2000) were excluded from these analyses because the dose of haloperidol (in mg) could not be obtained. Also, the Continuous Performance Test (CPT) was excluded from the stratification analysis because all four studies that reported the haloperidol dose were in the low dose category. Similarly, low vs. high dose contrasts could not be carried out for the Category Instance Generation Test (CIGT) because only one study was classified as high dose. In addition to examining associations between haloperidol dose and cognitive change, contrasts were carried out between studies that limited or did not limit recruitment to treatment refractory patients, and between studies that received or did not receive corporate sponsorship, excluding the Finger Tapping Test (FTT) for which insufficient data were available from studies without corporate sponsorship.

2.2. Analysis two: comparison of cognitive change with haloperidol to practice effects

2.2.1. Literature search and inclusion criteria for studies of practice effects

The same clinical trials included in Analysis One were included in Analysis Two. Relevant data on practice effects for a subset of the neuropsychological tests included in Analysis One (COWA, DSST, GPB, TMA, and TMB) were identified in three ways. 1) The primary source for identifying studies from which practice effects data could be extracted was the "Practitioner's Guide to Evaluating Change with Neuropsychological Assessment instruments" (McCaffrey et al., 2000). This volume consists of an extensive literature review of all studies published between 1970 and 1998 that examined longitudinal changes on over 70 commonly used neuropsychological assessment instruments. 2) Relevant test–retest data from the WAIS-R manuals was also included (Wechsler, 1981). 3) Literature searches of the computerized databases Medline and PsycInfo between the years 1998 and 2005 were also carried out. Key search parameters included combinations of the terms Cognition,

Neuropsychology, Neurocognition, Practice Effects, Longitudinal, and Prospective. Finally, the table of contents for the *Archives of Clinical Neuropsychology* and *The Clinical Neuropsychologist*, two journals that often publish studies on the psychometric properties of neuropsychological tests, were reviewed from January 1998 to July 2005.

Studies on practice effects were included if they met the following criteria: 1) inclusion of normal, healthy subjects free of any neurological or psychiatric illnesses between the ages of 18 and 65; 2) prospective study design with a baseline assessment and mean retest interval between 2 weeks and 1 year; 3) no intervention of any kind (i.e. pharmacological or surgical) occurred during the test–retest interval (data from placebo control groups was acceptable); 4) a baseline and follow-up sample size of at least 10; 5) results of neuropsychological change were reported for the COWA, CIGT, DSST, GPB, TMA, and TMB; and, 6) with the exception of test manuals, the study was published or 'in press' in a peer reviewed journal as of July 2005. 41 subject samples from 39 independent studies (including WAIS-R manual) met criteria and were included in the meta-analysis. The studies and tests included in each study are presented in Appendix 1 which is available as online supporting material. Practice effects studies were coded for author and year of publication, test–retest interval, age, and, when reported, the mean education and IQ of the sample.

2.2.2. Comparison of raw score changes for selected neuropsychological tests

The weighted and un-weighted mean difference between baseline and retest in raw score units was calculated for several neuropsychological tests to compare changes with haloperidol to practice effects. Raw score were used rather than effect sizes because group comparisons using effect sizes require comparable within group standard deviations (Shadish and Haddock, 1994), which may not be the case when comparing patients to controls, and to facilitate interpretation of the findings. Where necessary the WAIS-R manual was used to convert DSST scaled scores back to raw scores. CPT, FTT, WCST, and VLLi/VLLd were not included in this analysis due to the lack of practice effects data on the CPT, the limited number of clinical trials reporting FTT raw scores, the large variety of verbal list learning tests used in clinical trials, limited practice effects data on the WCST and evidence that test–retest reliability for the WCST may differ between control and clinical samples (for review see Spreen and Strauss, 1998; Lezak, 1995). For the weighted mean difference, the mean change in raw score units between baseline and follow-up was calculated for each study, weighted using the inverse variance method (Shadish and Haddock, 1994), and combined across studies. If the standard deviation of the mean change score was not reported and could not be derived from the reported statistics, it was estimated using the method described by Follmann et al. (1992). The un-weighted mean difference was simply the mean retest minus mean baseline test score averaged across studies. Contrasts between haloperidol and practice effects were carried out on the weighted and un-weighted mean change scores using weighted least squares (WLS) regression analysis and standard independent groups *t*-tests or non-parametric alternatives (Mann-Whitney *Z*-test) when indicated by a significant Levene's test ($p<.05$), respectively. In addition, differences between groups in baseline performance were examined using independent *t*-tests or a non-parametric alternative (Mann-Whitney *Z*-test) when indicated by a significant Levene's test ($p<.05$). The CIGT was not included in the baseline comparison because of slight differences between the versions of the CIGT used in clinical trials and practice effects studies. Specifically, most clinical trials used a three trail version of the CIGT (animal, fruits, and vegetable naming), whereas all practice effects studies used a single trial version (animal naming). Thus, mean scores at baseline could not be compared between groups since haloperidol studies reported the sum of scores across the three trials.

2.2.3. Moderator variable analysis

The effects of additional study characteristics including test-retest interval, education, IQ, and use of alternate test forms were examined within the set of practice effects studies to examine their compatibility with clinical trials of cognitive change in schizophrenia. Prior to carrying out the comparisons between haloperidol and practice effects described above, test–retest intervals were compared between groups using *t*-tests or non-parametric tests when appropriate for each neuropsychological test to ensure that they did not differ. Associations between test–retest interval, education, or IQ and neuropsychological test score changes were examined by correlation analysis within the set of practice effects studies to determine if these variables were associated with the magnitude of practice effects. In addition, group differences (practice effects studies vs. schizophrenia clinical trials) on these variables were also examined. Alternate forms exist for the COWA and were used somewhat frequently in studies classified as practice effects. Qualitative review suggests that alternate forms have little impact on the degree of change observed over

time on this test (Ruff et al., 1996; Zgaljardic and Benedict, 2001). Nonetheless, comparisons were carried out between studies that used alternate forms and those that did not within the set of practice effects studies prior to comparing haloperidol to practice effects.

3. Results

3.1. Analysis one: effect sizes for haloperidol

The combined and dose-stratified sample mean effect sizes and 95% confidence intervals, number of studies and subjects for the Global Cognitive Index and each neuropsychological test are presented in Table 3. The mean Global Cognitive Index effect size was significant (ES=0.18, Z=3.59, p<.001). Comparison between studies classified as low or high dose confirmed that studies classified as a high dose used a higher dose of haloperidol than studies classified as low dose (17.5± 6.6 vs. 6.8±2.6 mg, Z=2.88, p<.005). The mean Global Cognitive Index derived from low dose studies was not significantly different from high dose studies (ES=0.20 vs. 0.13; Q_{BET}=0.36, p<.548); although the mean Global Cognitive Index for low dose studies was significantly greater than zero (ES=0.20, Z=3.09, p<.002), but not for high dose studies (ES=0.13, Z=1.43, p<.154). The Global Cognitive Index was significantly correlated with haloperidol dose (r=−.75, p<.006). However, as shown in Fig. 1, this correlation was largely due to the presence of two outliers (Bilder et al., 2002; Buchanan et al., 1994) that used exceptionally high doses of haloperidol, 26.8 mg and 24.5 mg, respectively, compared to the remaining studies, range 2.9–15.5 mg. Removal of these two studies greatly diminished both the magnitude and significance of the correlation (r=−.18, p<.712). Schizophrenia classification (general vs. treatment refractory) was not related to the Global Cognitive Index and neuropsychological tests (ES=0.17 vs. 0.20, Q_{BET}=0.05, p<.820).

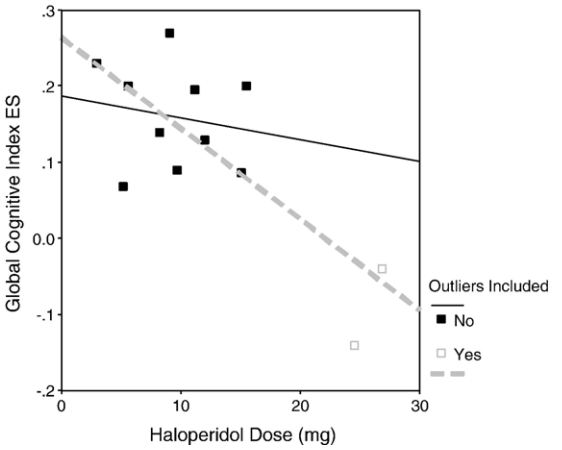

Fig. 1. Correlation between Global Cognitive Index effect sizes and haloperidol dose. The magnitude of the correlation (dashed grey line) with the two outliers included (grey markers) was −.75, p<.006. The magnitude of the correlation after excluding the two outliers (solid black line) was −.18, p<.712.

Table 3
Neuropsychological change with low dose (<10 mg) or high dose (>10 mg) haloperidol in controlled trials

Test	All haloperidol studies					Low dose haloperidol					High dose haloperidol				
	k	N	ES	95%CI	Test–retest Interval[a]	k	N	ES	95%CI	Test–retest Interval[a]	k	N	ES	95%CI	Test–retest Interval[a]
Global Cognitive Index	14	611	0.18[b]	.08–0.28	14.4 (11.0)	6	392	0.20[b]	0.07–0.33	8.0 (7.0)	6	173	0.13	−0.05–0.31	22.7 (19.0)
CPT	5	313	0.20[b]	0.05–0.35	9.6 (12.0)	4	294	0.22[b]	0.06–0.38	9.0 (10.0)	–	–	–	–	–
TMA	6	231	0.15	−0.03–0.33	8.3 (7.0)	2	151	0.07	−0.15–0.29	8.7 (8.0)	3	53	0.22	−0.16–0.60	9.0 (9.0)
DSST	9	475	0.13[b]	0.01–0.25	18.4 (12.0)	5	344	0.13	−0.02–0.28	30.5(28.0)	4	131	0.13	−0.09–0.35	8.8 (8.0)
TMB	11	384	0.09	−0.04–0.23	15.6 (10.0)	4	179	0.02	−0.18–0.22	7.5 (7.0)	6	178	0.12	−0.08–0.32	22.7 (19.0)
WCST	10	491	0.02	−0.10–0.14	15.6(11.0)	6	359	−0.01	−0.16–0.13	8.0 (7.0)	4	132	0.12	−0.11–0.33	27.0 (23.0)
VLLi	11	538	0.32[b]	0.19–0.43	15.8 (12.0)	6	371	0.37[b]	0.23–0.51	8.0 (7.0)	5	167	0.20[b]	0.00–0.40	25.2 (24.0)
VLLd	7	420	0.27[b]	0.14–0.40	14.5 (8.0)	3	252	0.22[b]	0.05–0.39	8.7 (8.0)	3	141	0.28[b]	0.06–0.50	23.3 (14.0)
COWA	12	553	0.05	−0.07–0.17	15.4 (11.0)	6	372	0.04	−0.10–0.18	8.0 (7.0)	5	154	0.00	−0.21–0.21	26.4 (24.0)
CIGT	5	349	−0.09	−0.24–0.06	9.5 (10.0)	4	330	−0.06	−0.21–0.09	9.5 (10.0)	1	19	−0.68	−1.33–0.05	10.0 (10.0)
FTT	4	128	−0.05	−0.30–0.20	16.0(13.0)	2	92	−0.06	−0.35–0.23	9.0(9.0)	2	36	−0.04	−0.50–0.43	23.0 (23.0)
GPB	5	196	0.01	−0.17–.019	20.4 (8.0)	3	104	−0.08	−0.34–0.18	6.0 (6.0)	2	92	0.09	−0.17–0.35	42.0 (42.0)

Number of effect sizes (k), number of subjects (N), mean effect size (ES), and test–retest interval in weeks.
[a] Mean (median) in weeks.
[b] Effect size significantly greater than 0.

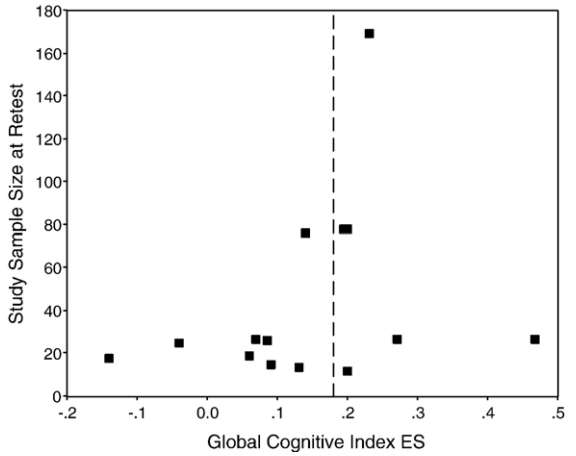

Fig. 2. Funnel plot of Global Cognitive Index effect sizes. This scatter plot graphs effect size for the Global Cognitive Index on the *X*-axis with study sample size at retest on the *Y*-axis. In the absence of publication bias, the shape of the plot should resemble an inverted funnel with effect sizes derived from studies with smaller sample sizes demonstrating greater variability than studies with larger sample sizes. The shape of the funnel plot for the studies included in current meta-analysis roughly approximates an inverted funnel arguing against the presence of significant publication bias.

Corporate sponsorship (yes vs. no) was also unrelated to Global Cognitive Index effect sizes (ES=0.20 vs. 0.16, $Q_{BET}=0.15$, $p>.698$). In addition, corporate sponsored studies did not use a significantly higher dose of haloperidol than studies that were independently funded (9.0±4.5 vs. 15.3±8.7, $t(10)=1.59$, $p<.145$). Examination of the funnel plot presented in Fig. 2 does not indicate the presence of significant publication bias. In general, studies with larger sample sizes yielded effect sizes closer to the mean, whereas studies with smaller sample sizes yielded more variable effect sizes that were roughly distributed evenly above and below the mean effect size.

For specific neuropsychological measures, the mean effect sizes for CPT (ES=0.22), DSST (ES=0.13), VLLi (ES=0.31), and VLLd (ES=0.27) were significantly greater than zero. No studies classified as low dose yielded larger effect sizes for any neuropsychological measure. A significant inverse correlation between dose and VLLi effect sizes was observed ($r=-0.63$, $p<.041$). No additional significant correlations were observed between haloperidol dose and change on specific neuropsychological tests. The effect sizes for VLLi and VLLd remained significant when the analysis was restricted to studies that used alternate test forms (VLLi: ES=0.28, $Z=2.89$, $p<.004$; VLLd=0.27, $Z=3.98$, $p<.001$). No effect size was calculated using the random effects model. The moderator variables schizophrenia classification and corporate sponsorship were not associated with any neuropsychological measure.

3.2. Analysis two: comparison of cognitive change with haloperidol to practice effects

3.2.1. Practice effects: moderator variable analysis

No significant correlations were observed between practice effects and test–retest interval, age, IQ, or education on any neuropsychological test within the set of practice effects studies. The mean re-test interval did not differ between haloperidol and practice effects studies for any neuropsychological test. The mean age of the subjects included in practice effects studies did not differ from the mean age of patients included in the haloperidol arms of clinical trials (38.7±11.8 vs. 34.6±6.7; $Z=0.87$, $p<.387$). The 23 practice effects studies reporting the mean education of the subjects included was significantly greater than the mean education level derived from the 7 haloperidol studies that reported education level (13.6±1.6 vs. 12.0±0.7; $t(28)=2.55$,

Table 4
Raw score changes on selected neuropsychological tests with haloperidol compared to practice effects

Test	Haloperidol							Practice effects						
	k	N	Weighted		Un-weighted		Test–retest interval[a]	*k*	N	Weighted		Un-weighted		Test–retest interval[a]
			Mean	95% CI	Mean	95% CI				Mean	95% CI	Mean	95% CI	
TMA	6	231	3.2	−3.6–9.7	9.1	−3.3–21.5	8.3 (7.0)	18	785	2.0	1.1–2.9	4.2	3.0–5.3	16.2 (7.0)
DSST	7	384	0.9[b]	−0.1–1.8	0.7[b]	−0.6–2.0	11.7 (12.0)	13	581	3.5	2.7–4.2	3.2	2.2–4.2	10.8 (4.5)
TMB	8	324	8.9	−0.1–17.9	14.5	0.8–28.3	15.7 (10.0)	21	981	4.7	3.4–5.9	6.4	4.5–8.3	15.6 (8.0)
COWA	11	542	0.3[b]	−3.5–1.1	0.9[b]	−0.5–2.3	14.0 (10.0)	16	769	2.7	2.0–3.4	2.7	1.7–3.7	15.4 (4.0)
CIGT	5	349	−0.7	−2.3–0.9	−1.8	−7.0–3.5	9.6 (10.0)	4	144	0.8	−0.9–2.4	0.0	−1.6–1.5	17.5 (7.0)
GPB	4	185	0.5	−7.8–8.8	1.7	−7.7–11.0	29.5 (30.0)	4	698	2.4	1.5–3.3	2.5	1.9–6.9	16.5 (16.0)

[a] Mean (median) in weeks.
[b] Significantly different than practice effects.

$p<.018$). Mean IQ for practice effects studies reported was higher than the mean IQ for haloperidol studies (108.7±5.9 vs. 74.6±31.6; Mann-Whitney $Z=3.00$, $p<.004$). However, this finding should be interpreted cautiously as only 4 out 14 clinical trials and 15 out of 39 practice effects studies reported mean IQ. The degree of practice effects observed on the COWA was approximately the same for studies that used alternate forms compared to those that did not (WLS: 2.3 vs. 2.9, $F<0.68$, $p<.426$; t-test: 1.7 vs. 3.3, $t(14)<1.82$, $p<.100$). As such, COWA scores were combined across practice effects studies regardless of whether or not alternate forms were used.

3.2.2. Cognitive change with haloperidol compared to practice effects

The weighted and un-weighted mean change scores, 95% confidence intervals, and test–retest intervals of each neuropsychological test for haloperidol and practice effects are presented in Table 4. Both the weighted mean and un-weighted mean COWA and DSST change scores with haloperidol were less than practice effects (COWA: WLS $F(1,25)=15.59$, $p<.002$; $t(25)=2.31$, $p<.030$; DSST: WLS $F(1,18)=19.78$, $p<.001$; $t(18)=3.36$, $p<.004$). Scatter plots showing the improvement observed in each study for DSST and COWA are presented in Fig. 3. No significant differences were observed on any of the remaining tests. At baseline, studies of practice effects reported significantly higher scores for all neuropsychological tests than haloperidol clinical trials, with the exception of the CIGT which was excluded from this analysis. The means at baseline for each test in the haloperidol and practice effects groups are presented in Table 5 of the online supporting material.

4. Discussion

The present study details the effect of haloperidol on cognitive performance in patients with schizophrenia assigned to receive haloperidol in clinical trials comparing haloperidol to an atypical APD. The analyses were undertaken to quantitatively address several important threats to the validity of prior assertions that atypical APDs directly improve cognitive skills in schizophrenia. Contrary speculation has attributed the apparent benefit of atypical APD to an indirect benefit derived from an avoidance of the detrimental effects of typical APD or to avoidance of inappropriately high doses of typical APDs. If accurate, this speculation would undermine the attribution of benefits to the atypical APD along with pharmacological models, such as enhanced DA release in the prefrontal cortex, developed to account for the apparent benefit. The results of this analysis provide some support for the indirect-action hypothesis, but not at a level that challenges the overall direct hypothesis.

An important prediction of the indirect-action hypothesis is that cognitive benefits would not be observed with haloperidol, and that the absence of benefit would be most robust with higher doses of the medication. The current results provided only circumstantial support for these hypotheses. Patients receiving haloperidol in atypical vs. typical APD clinical trials demonstrate improvements relative to baseline scores on tests of attention, processing speed, and new verbal learning and memory. In most cases the mean effect sizes are

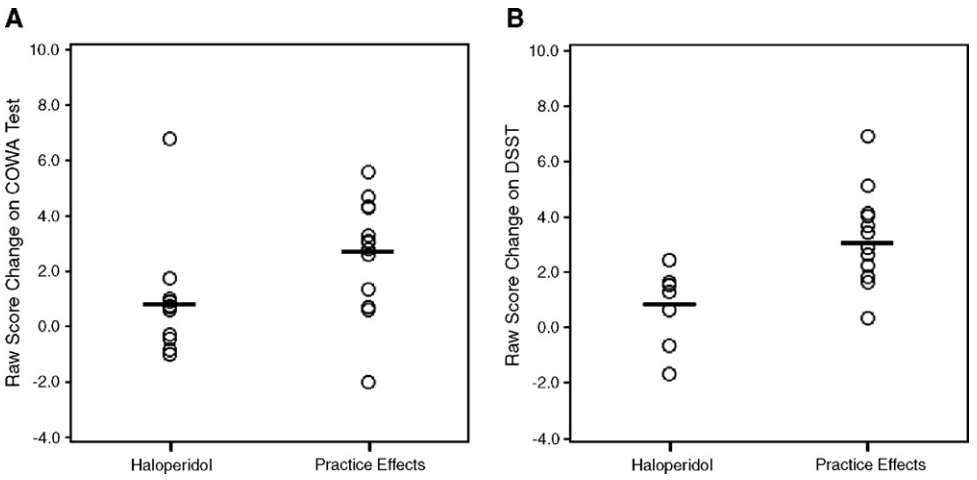

Fig. 3. Raw score changes on the (A) COWA and (B) DSST with haloperidol compared to practice effects. Solid black line represents the un-weighted mean change score within each group.

remarkably similar between studies that used a low dose of haloperidol (<10 mg) and those that used a higher dose (>10 mg). In contrast, correlation analyses identified an inverse relationship between haloperidol dose and improvement in overall cognitive function and change on tests of verbal learning. However, it was clear that the inverse correlation observed between haloperidol dose and change in overall cognitive function was due to two studies (Buchanan et al., 1994; Bilder et al., 2002) that used exceptionally high doses of haloperidol (24.5 and 26.8 mg, respectively) compared to the range used in the remaining studies (2.9 to 15.5 mg). Thus, for the most part, these findings do not support speculation that some clinical trials of atypical APDs vs. haloperidol were biased towards identifying positive effects of atypical APDs on cognition because they utilized too high a dose of haloperidol in the control arms. Nonetheless, the available data suggests that doses approaching or exceeding 25 mg may be associated with less cognitive improvement, or slight decrement, and patients receiving such a high dosing are an inappropriate comparison group for studying the cognitive effects of atypical APDs. There was no evidence that corporate sponsorship influenced effects for cognitive change with haloperidol or that corporate sponsored studies used higher doses of haloperidol in the control arms of atypical vs. typical APD clinical trials.

The current results from Analysis One are similar in many respects to the meta-analysis of cognitive change with typical APDs carried out by Mishara and Goldberg (2004), despite the fact that only one clinical trial included in the current review was also included in the earlier meta-analysis. The effect size for overall cognitive change with haloperidol reported herein was 0.18, which is consistent with the 0.22 improvement identified for typical APDs as a class reported by Mishara and Goldberg (2004). Moreover, consistent with Mishara and Goldberg (2004), studies classified as high dose did not yield larger effect sizes for change in overall cognitive function, although the present data adds the important caveat that extremely high dosings may have a negative impact. In contrast to the Mishara and Goldberg (2004) meta-analysis, we also examined dose effects on specific neuropsychological tests. This revealed a specific negative effect of dose on verbal list learning, which differed from the majority of cognitive domains, which showed little impact of dose.

A second prediction of the indirect-action hypothesis is that haloperidol masks the normal performance gains anticipated from repeated presentation of a neuropsychological instrument, thus resulting in apparent atypical APD improvements that are nothing more than normal practice effects. The present analysis offered weak support for this hypothesis. Most of the instruments with data available for comparison (TMA, TMB, CIGT, GPB) gave no indication of practice effects different from the normative samples. Caution is warranted when interpreting the results for the CIGT though as practice effects estimates for this test were based on the single trail version, whereas most clinical trials used a three trial version. Thus, it is possible that the improvement might have reached significance on the three trial version, although this seems unlikely given that the unweighted mean raw score improvement on the single trial version was exactly zero. The DSST and the COWA, however, produced less change in the haloperidol arms compared to the improvement expected from the normative samples. Although slight improvement was observed on the DSST in the haloperidol groups, it was diminished relative to normal. The COWA did not show improvement in the haloperidol groups, and this was less than the gain observed in the normative samples. Thus, although haloperidol does not cause a generalized deficit in the ability to learn from prior exposure, it may contribute to circumscribed reductions in the practice effects observed on a test of visuomotor tracking with translation (DSST) and on a test of verbal fluency (COWA).

There are several important caveats to the application of normative practice effects data to clinical trials comparisons that must be noted. First, it is possible that the absence of expected practice effects on the COWA and DSST in patients receiving haloperidol is a reflection of the illness rather than a consequence of treatment. Several findings argue against this. In the largest study of its kind, Heaton et al. (2001a) examined longitudinal changes on over 20 neuropsychological tests, almost all of which were included in our meta-analysis, in a sample of 142 schizophrenia patients and 206 controls. They found that patients demonstrated the same degree of change over approximately 16 months. Moreover, no differences in practice effects were observed between patients and controls when subjects were stratified by short or long test–retest intervals. Similarly, two smaller investigations that included first episode, drug naive patients by Fagerlund et al. (2004) and Hill et al. (2004) also found that patients show the same degree of change as matched control samples on many of the same neuropsychological tests included in the current review after test–retest intervals of 13 and 6 weeks, respectively. Taken together, these findings suggest that at the group level, patients with schizophrenia and controls demonstrate comparable practice effects on the measures included in our meta-analysis. In

fact, one double-blind, random assignment study of 21 patients found that patients withdrawn from haloperidol for three weeks actually demonstrated less improvement on the WMS-R General Memory index, but not on the TMA and TMB tests of attention, than patients maintained on a stable dose of haloperidol (Gilbertson and van Kammen, 1997). In contrast, Hill et al. (2004) found that neuroleptic naive patients did not demonstrate any improvement in verbal learning and memory following six weeks of treatment with either haloperidol or risperidone, a finding that is incongruent with the results reported by Gilbertson and van Kammen (1997) and the results from Analysis One reported in the current review which found robust improvement on tests of verbal learning and memory with haloperidol, even when alternate test forms are used. Thus, there is conflicting evidence as to whether or not changes in verbal learning over time reflect an improvement associated with haloperidol, normal practice effects, or a reduction in normal practice effects associated with illness itself. Regardless, the ambiguity surrounding prospective changes in verbal learning and memory has little bearing on the results reported herein from Analysis Two given that tests of learning and memory were not included in the practice effects comparison and that considerable evidence suggests that patients demonstrate intact practice effects on the remaining neuropsychological measures included in the meta-analysis.

In addition to the ambiguities potentially introduced by the disease state, the suitability of a comparison between normative retest results and prospective assessments within clinical trials may be influenced by test–retest interval, age, type of test (i.e. learning and memory or psychomotor), and possibly overall cognitive ability and education (Dikmen et al., 1999; Heaton et al., 2001b; Temkin et al., 1999). In general, tests of learning and memory are especially vulnerable to practice effects particularly when test–retest intervals are short; although the use of alternate test forms can substantially reduce and even eliminate practice effects on some measures (Benedict and Zgaljardic, 1998). However, for tests other than learning and memory, test–retest interval appears to exert only a minimal effect on the degree of practice effects demonstrated, at least at intervals ranging from several weeks to months (Levine et al., 2004; Dikmen et al., 1999; Basso et al., 2002). For example, practice effects on the WAIS-III are similar in magnitude after 3 or 6 month test–retest intervals (Basso et al., 2002). The absence of significant correlations between practice effects and test–retest intervals among the studies included in the current meta-analysis is consistent with these findings. It is unlikely though that differential practice effects over varying retest intervals influenced the current results given that test–retest intervals were comparable between haloperidol and practice effects studies for each neuropsychological test included in Analysis Two. The effects of additional factors such as age, education, and overall cognitive ability on practice effects are less well understood. There is evidence that older subjects may demonstrate less practice effects than younger subjects, and subjects with greater overall cognitive ability or more education may demonstrate greater practice effects than subjects with less education and lower overall cognitive abilities (Dikmen et al., 1999; Heaton et al., 2001b); although the effects of these two variables appear to account for only a very small proportion of the variance in practice effects (Levine et al., 2004; Salinsky et al., 2001). The fact that patients included in the haloperidol studies had significantly lower overall cognitive function (as indicated by IQ) and less education than subjects included in the normative samples of practice effects may suggest that the practice effects estimated here overestimated the degree of practice effects expected in schizophrenia patients. However, available evidence suggests otherwise. Specifically, Heaton et al. (2001a,b) did not identify any difference in practice effects between controls and patients, despite the fact that patients demonstrated a significant deficit in overall cognitive function and were significantly less educated compared to controls. Moreover, no differences in practice effects were observed even when patients were stratified into low and high functioning groups at baseline. Similar findings were reported by Fagerlund et al. (2004) and Hill et al. (2004) in neuroleptic naïve patients retested after intervals of 13 and 6 weeks, respectively. The fact that cognitive change with haloperidol was less than practice effects on only two measures suggests that even if the practice effects calculated here are inappropriately high, the effects of haloperidol on practice effects appear rather mild and limited to two tests.

We believe the results from this meta-analysis are informative, despite the caveats mentioned above. At the very least the results indicate that, contrary to alternate hypotheses, and consistent with a recent, more general meta-analysis of cognitive improvement with typical APDs as a class, cognitive improvement does occur with haloperidol in atypical vs. typical APD clinical trails and that, with the exception of two out of six neuropsychological tests, improvement with haloperidol is equivalent to practice effects. The putative deleterious effects of haloperidol, relative to estimated practice effects are small in magnitude, ranging from approximately two to

four words on the COWA and approximately two items on the DSST, and appear to be unrelated to clinically relevant doses used to treat schizophrenia. Nonetheless, the results of atypical APD vs. haloperidol trials may have been biased towards identifying a slightly larger benefit with atypical APDs on these two commonly used neuropsychological tests, especially given the apparently subtle pro-cognitive effects of atypical APDs on some neuropsychological instruments. The absence of a relationship between haloperidol dose and cognitive change on these two measures might suggest that haloperidol may impede practice effects on these two measures regardless of the dose used. The existing literature on medication effects in schizophrenia has only rarely attempted to address issues relating to practice effects. The present data suggests that actually estimating such effects can help illuminate current controversies in neuropsychopharmacology.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2006.08.021.

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