TITLE: Bupropion for Adults with Attention Deficit Hyperactivity Disorder: A Review of the Clinical Effectiveness and Harms of Misuse

DATE: 21 June 2010

CONTEXT AND POLICY ISSUES:

Attention deficit hyperactivity disorder (ADHD) is frequently considered a disorder of childhood, however, approximately 50% of children with ADHD have symptoms that persist into adulthood.\(^1\) A recent nationwide study from the US estimated the prevalence of ADHD in adults to be 4.4%.\(^2\) Adults with ADHD are more likely than the general population to have a diagnosed psychiatric comorbidity, including anxiety, bipolar disorder, depression, and drug or alcohol abuse.\(^3\)

Practice guidelines produced by the Canadian ADHD Resource Alliance (CAADRA)\(^4\) recommend both long-acting stimulant (e.g., methylphenidate and mixed amphetamine salts) and non-stimulant (e.g., atomoxetine) medications as first-line treatment for adults with ADHD. CAADRA further provides information about several “off-label” medications, suggesting that bupropion may be useful in situations of comorbid depression, and that it is free of the risk of abuse or diversion.\(^4\)

In Canada bupropion is approved for treatment of major depressive illness and as a smoking cessation aid. Marketed products for major depressive disorder include both sustained release (SR) and extended release (XL) products designed for twice or once daily dosing respectively (Wellbutrin-SR and Wellbutrin-XL). The marketed product for smoking cessation is a sustained release product designed for twice daily dosing (Zyban).

Since methylphenidate is a sought-after drug in the prison population, and amphetamines may be expected to be similarly sought after, it is reasonable to consider alternative agents in this situation. This report reviews the evidence for efficacy of bupropion in adults with ADHD, and for harms associated with inappropriate use.

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RESEARCH QUESTIONS:

1. What is the clinical effectiveness of bupropion for adults with attention deficit hyperactivity disorder?

2. What are the harms associated with the misuse of bupropion?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including Ovid Medline, Ovid Embase, Ovid PsycINFO, PubMed, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2000 and May 19, 2010. No filters were applied to limit the retrieval by study type.

Since a number of recent systematic reviews and randomized controlled trials (RCTs) relevant to question #1 were identified, the search period was subsequently restricted to January 1, 2005 to May 19, 2010. For question #2 relevant publications from the full 10-year search were included; however, case reports were only included if they were relevant to nasal insufflation.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews, and meta-analyses are presented first. These are followed by observational studies.

SUMMARY OF FINDINGS:

The search identified two published systematic reviews that specifically examined the use of bupropion for treatment of ADHD.5,6 Three relevant randomized controlled trials (RCTs)7-9 identified in the search were included in both of the systematic reviews and therefore are not further summarized in this report. One observational study relevant to the efficacy of bupropion for ADHD was identified and summarized.10 Finally, ten publications of descriptive observational studies relevant to bupropion misuse were identified and summarized. These included five publications of four observational studies providing harms information associated with misuse of bupropion11-15, and five case reports specific to nasal insufflation of bupropion.16-20.

No health technology assessments were identified in the search.

Systematic reviews and meta-analyses

Verbeeck et al. 20095

The objective of this systematic review was to examine the efficacy of antidepressants in the treatment of adult ADHD in comparison to placebo (Appendix 1, Table 1). The literature search, which was narrow in scope (bibliographic databases), identified eight placebo-controlled trials. Five of the trials included bupropion; four employed the SR form and one employed the XL form. Of the five bupropion trials, three7-9 were identified in our literature search and two fell outside the search limit.
All five included bupropion trials were reportedly double blind (DB) parallel-group RCTs conducted in outpatients. None of the five trials could be considered high-quality since details of randomization and adequacy of treatment allocation were missing in all cases. Further, loss to follow-up, ranging from 18% to 30% in the three trials identified in our literature search, may have biased study results. The five studies included a total of 389 patients (range of 30 to 162); study duration (range six to 12 weeks), publication year (range 2001-2006), mean age (range 32 to 40 years), percent male (range 55% to 73%). Four trials specifically excluded patients with comorbid psychiatric illness and a recent history of substance abuse. However, one trial specifically enrolled patients with a history of substance abuse currently maintained on methadone, although patients with comorbid psychiatric illness were excluded. Three trials titrated the bupropion dose to a maximum of 400mg/day, and two trials titrated the dose to a maximum of 300mg/day.

Included studies employed a variety of efficacy measures including: the Attention Deficit Disorder Rating Scale (ADHD-RS), the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), the Connors’ Adult ADHD Rating Scale (CAARS), and the Clinical Global Impression of Improvement (CGI-I). Since all studies employed the physician based CGI-I, this outcome was the basis of the pooled analysis; a comparison of the proportion of patients achieving clinical improvement (classified as “much” or “very much” improved on the CGI-I scale) was performed. Based on the pooled analysis, Verbeeck et al. 2009 reported that patients receiving bupropion were statistically more likely to experience clinical improvement compared with patients receiving placebo; odds ratio (95% confidence intervals [CI]) = 2.42 (1.09, 5.36). Within the individual studies, the odds of greater clinical improvement were not statistically different between bupropion and placebo; however, this is likely related to their small sample sizes. Of note, the non-statistically significant effect sizes in the individual trials favoured bupropion in four trials, however, in the trial that enrolled methadone-maintained patients the non-statistically significant effect size favoured placebo. In addition to the pooled analysis of CGI-I results it was noted that of four trials reporting changes in ADHD symptoms using the ADHD-RS, two reported statistically significant improvement with bupropion compared to placebo, and two reported no statistical difference between bupropion and placebo. The remaining trial reported no statistical difference in ADHD symptoms between bupropion and placebo based on the WRAADDS.

The systematic review had a number of limitations including a failure to search for unpublished data, no evidence of duplicate data extraction, and pooling of data from only one subjective efficacy outcome. It was difficult to assess the internal validity of individual trial results due to the lack of information regarding the adequacy of randomization and allocation concealment techniques. Further, loss to follow-up may have biased the estimate of effect. However, the trend toward greater improvement with bupropion compared to placebo across all trials (except the trial enrolling methadone-maintained patients) enhances confidence in this finding. The external validity of the bupropion trials (the degree to which the results may be generalized to a wider population) is compromised by the exclusion of patients with psychiatric comorbidities from all trials, and the exclusion of patients with a history of substance abuse from all but one trial. Finally, included trials were of short duration and there was a lack of data related to quality of life and functional outcomes (e.g., school or work performance).
The objective of this systematic review was to compare the efficacy and safety of commonly used, newer ADHD drugs (non-stimulants and longer-acting stimulants) with conventional shorter-acting stimulants (Appendix 1, Table 2). The literature search targeted both published and unpublished trials, employing a search of bibliographic databases, reference lists of included studies, and requests to manufacturers. Twenty-two trials were identified, employing a number of therapeutic agents including methylphenidate (11 trials), amphetamines (four trials), bupropion (four trials), atomoxetine (three trials), and dexmethylphenidate (one trial). Of the four bupropion trials, three \(^7\text{-}^9\) were identified in our literature search, and one fell outside the five-year search limit. All four trials were also included in the systematic review by Verbeeck et al. \(^5\)

One of the four trials, which specifically enrolled methadone-maintained patients was a three-arm trial \(^7\) that included bupropion, methylphenidate, and placebo; however, for an unspecified reason, only the methylphenidate and placebo arms were included in the systematic review. Thus, only three trials actually contributed bupropion data.

The twenty-two studies reported data for 2203 patients (range 22 to 280), with a mean age of 38 years, 59% of which were male; study duration ranged from two to 20 weeks, and year of publication from 1985-2007. The three studies contributing bupropion data involved 261 patients (range 40 to 162); mean age (range 34 to 40 years), percentage male (range 55% to 73%), study duration (range six to eight weeks), and publication year (range 2001-2005). Data were pooled according to drug class (short-acting stimulants, long-acting stimulants, atomoxetine, and long-acting bupropion) for comparisons to placebo. Further, since the included trials compared active treatments to placebo the authors performed indirect between-treatment comparisons to estimate differences between drug classes.

Clinical response was the basis of the pooled analysis, however the definition of response varied between trials; the definition of response in the bupropion trials was ≥30% reduction in the ADHD-RS (two trials) and ≥50% reduction in the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (1 trial). Based on the pooled analysis, patients receiving long-acting bupropion were statistically more likely to respond to treatment compared with patients receiving placebo; relative risk (95% CI) = 1.87 (1.36, 2.58). However, based on an indirect comparison, patients receiving short-acting stimulants were more likely to respond to treatment compared with patients receiving long-acting bupropion; relative risk ratio (95% CI) = 2.24 (1.23, 4.08).

The above systematic review appears well conducted, including a search for published and unpublished literature, study selection and data extraction by two independent researchers, and appropriate statistical methods. Its major limitation is the reliance upon indirect comparison methods employing placebo-controlled trials to estimate differences between drug classes. Head-to-head trials, if available, would provide more valid estimates of the difference in efficacy between drug classes. Further, little information was provided regarding patient characteristics of included trials. Differences in disease severity, disease subtype, and comorbidities could confound the estimates of effect; individual review of the non-bupropion trials is beyond the scope of this HTIS request. Since the bupropion trials included in this systematic review were also included in the Verbeeck systematic review the previously mentioned limitations related to the internal validity of the bupropion versus placebo findings remain (e.g., frequent loss to follow-up, unclear adequacy of randomization and allocation concealment techniques). Further,
concerns regarding the limited generalizability and the lack of clinically important real-world outcomes in the bupropion trials remain.

**Observational studies**

Wilens et al. 2009\(^{10}\) report the findings of a small \(n=32\) six-week non-comparative trial examining the efficacy and tolerability of bupropion SR in adults with ADHD and substance use disorder (SUD). Eligible patients were 18 to 55 years with a diagnosis of both ADHD and SUD based on the Diagnostic and Statistical Manual of Mental Disorders 4\(^{\text{th}}\) edition (DSM-IV). Patients with unstable medical or psychological disorders were excluded. All patients were treated with forced titration of bupropion SR, starting at 100mg once daily, titrated to 200mg twice daily over the first four weeks. Symptom scores at six weeks were compared to baseline scores for the intention to treat population, with last observation carried forward for patients with missing data. Fifty-nine percent of patients completed the six week trial. At endpoint, reductions from baseline in the ADHD-RS, and the Clinical Global Impression of Severity (CGI-S) scores were statistically significant; the reductions were felt to be clinically important. Further, 41% of patients were considered improved; CGI-I scores of 2 or 1, much or very much improved respectively. In terms of SUD, 31% of patients were considered improved at endpoint, however there was no clinically or statistically significant difference in the proportion of patients reporting substance use at endpoint compared with baseline. The investigators concluded that bupropion SR treatment is associated with clinically important reductions in symptoms of ADHD but not SUD. Given the lack of a control group this study constitutes poor quality evidence for the therapeutic effect of bupropion.

Belson and Kelly, 2002 reported the results of a retrospective observational study of the demographics, clinical effects, and outcomes of bupropion-only exposures (i.e., no co-ingested substances) reported to poison control centres.\(^{15}\) Data was retrieved from the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centres for the years 1998 and 1999; only reports of bupropion ingestion were reviewed (no other routes of administration). A total of 7348 reports of bupropion-only exposure were identified; Wellbutrin SR (3755 or 51%), Wellbutrin (2184 or 30%) and Zyban (1409 or 19%). The majority of reports (69%) involved adolescents or adults. Of all reports, 2424 (33%) were intentional, including suspected suicide (29%), misuse (2%), abuse (1%) and unknown (1%). Overall, the most commonly experienced clinical effects were tachycardia (9%), drowsiness/lethargy (7%), seizure (6%), agitation (5%), and vomiting (4%); vomiting was most common in children and tachycardia was most common in adolescents and adults. Cardiac toxicity other than tachycardia was uncommon. Many of the common adverse events were neurological. Seizures, the majority of which were single, occurred in 15% (361/2424) of patients with intentional exposure. Death occurred in five reported exposures, all of which were suspected suicides. The above study is limited by the lack of dosage information.

Shepherd et al. 2004 reported the results of a retrospective study to describe the clinical course of intentional bupropion overdose in adults and adolescents.\(^{12}\) Cases were identified from the reports to the Texas Poison Centre Network during the years 1998 and 1999. A total of 385 cases were identified, two of which resulted in death. The authors report the following frequencies of common adverse events: tachycardia (23%), gastrointestinal upset (14%) and seizures (11%). It is unclear if this represents the frequency in all 385 cases or just those patients for whom data was available, since it was noted that there was a lack of outcome data
for 28% (n=108) of cases identified. Of the 385 cases, 99 (26%) were reported to have a moderate, major, or fatal outcome. Among patients with at least a moderate outcome (n=99), those who experienced seizures were more likely to have ingested greater than 2.5 g of bupropion compared to those who did not experience seizure; 51% (21/41) versus 14% (8/58). Of the 41 cases experiencing seizure, nine (22%) experienced more than one seizure, and 1 (2%) developed status epilepticus. The time between ingestion and seizure ranged from one to 14 hours (mean [SD] = 4.2 [3.2]) for the 28 cases in which ingestion time was considered reliable.

Starr et al. 2009 reported the results of a combination retrospective/prospective observational study of bupropion extended release (XL) overdoses, to determine a minimum emergency department observation time for the occurrence of seizure and to identify symptoms that may predict seizure. Data were obtained retrospectively (one year) and prospectively (two years) for the period January 2005 to December 2007 from five poison centres in the US. Eligible records were for patients with a minimum bupropion XL ingestion of ≥600 mg for patients ≥12 years, or ≥4 mg/kg in patients <12 years. In addition patients were required to have been followed in-hospital for a minimum of 24 hours and have a documented outcome. Ineligible records were those in which patients had: co-ingestions with unknown substances or substances known to lower the seizure threshold or suppress seizures, a history of seizure disorder, a positive cocaine or benzodiazepine screen, or substance dependence. A total of 117 patient records (100 adolescents/adults and 17 children) met the inclusion criteria, of which 97 (83%) did not indicate a co-ingestion. The mean (SD) dose was 4318 (6526) mg for adults/adolescents, and 36 (42) mg/kg for children. Seizures occurred in 37 (32%) with a mean onset after ingestion of 7.3 (5.4) hours; range 0.5-24 hours. Eighteen (49%) patients experienced a second seizure, which occurred on average 2.6 hours after the first seizure (range: immediate to 14 hours). High negative predictive values were observed for common symptoms of bupropion overdose, tachycardia (93%), agitation (73%), tremors (76%) and hallucinations (71%), indicating that seizure is unlikely in the absence of these symptoms. The positive predictive values for the above symptoms were more modest, thus the presence of any one symptom does not well predict seizure. Based on the above the authors recommended an observation period of at least 24 hours following ingestion of bupropion XL.

Balit et al., 2003 reported the results of a prospective study in Australia to investigate the toxicity of bupropion in deliberate self-poisoning in adults and accidental ingestion by children.14 Calls to the New South Wales Poison Information Centre from hospitals regarding bupropion ingestion, for the period November 1, 2000 to July 31, 2001, were linked to patient hospital records. A total of 69 calls were identified, 59 for adults and 10 for children. Forty-five of 59 adult calls could be linked to hospital records, the results of which are reported below. Of the 45 adults, 19 had ingested only bupropion and 26 had ingested multiple agents. The mean (SD) dose of bupropion was 5.1 (4.8) grams. Common clinical effects reported for bupropion-only ingestion were tachycardia (83%), hypertension (56%), seizures (37%), gastrointestinal symptoms (37%) and agitation (32%). The frequency of seizure increased with increased bupropion ingestion; 0-30 tablets (18%, 5/28), 31-60 tablets (50%, 5/10) and >60 tablets (100%, 6/6); this finding was consistent for both bupropion only and bupropion with co-ingestants. There were no deaths in this study. Isbister and Balit, 200313 further compared electrocardiograms (ECGs) from 17 of the above adult patients to ECGs from a control group (n=318) comprised of patients presenting to a regional toxicology unit with single ingestions of acetaminophen, temazepam, oxazepam, or diazepam (drugs with no known ECG effects). ECGs from bupropion patients were excluded if
patients had co-ingested a medication known to have cardiovascular effects or known to affect
the QT interval. Bupropion patients had a statistically longer corrected QT (QTc) interval
compared with the control group, however the uncorrected QT and QRS intervals did not differ
between the bupropion and control groups. The authors note that the between group differences
in the QTc may be due to the fact that the correction formula for calculation of the QTc
overcorrects in the presence of tachycardia, which was common in the bupropion patients. The
authors further noted that the clinical significance of the QTc prolongation is unclear.

Case reports of nasal insufflation

Welsh, 2002\(^\text{20}\) reported the case of a 16 year-old male who presented to the emergency
department following a tonic-clonic seizure. The patient’s medication history contained only
bupropion 150 mg (Wellbutrin SR) twice daily for depression. The patient admitted to crushing
six 150 mg tablets of Wellbutrin and insufflating them one hour prior to the seizure. He denied
other illicit substance use but volunteered that on previous occasions two to three tablets had
provided a “brief buzz”.

Kim and Steinhart, 2010\(^\text{16}\) reported the case of a 38 year-old male who presented to the
emergency department following a witnessed seizure. He had a history of approximately one
seizure per month over the last several months. The patient’s medication history contained
glyburide, metformin, olanzapine, and bupropion; the indication for bupropion use was unclear.
The patient admitted to crushing 15 bupropion 100 mg SR tablets and insufflating them but
denied recent alcohol or other recreational drug use. The patient admitted to cocaine use
approximately four months earlier; he indicated he had learned about bupropion insufflation
during a recent incarceration and that it provided him with a chemical euphoria similar to
cocaine.

Kurshid, 2004\(^\text{19}\) reported the case of a 15 year-old female admitted to an inpatient psychiatric
unit due to increased irritability, impulsivity and aggression over the previous two weeks. The
patient’s medication history contained albuterol inhaler for asthma, and bupropion for ADHD.
The patient admitted to several occasions of nasal insufflation of crushed bupropion tablets over
the previous weeks (unspecified dosage or number of tablets) from which she reported a “buzz”
similar to marijuana but lasting only a few seconds.

Hill et al. 2007 reported the case of a 50-year-old who presented at the emergency department
following a seizure. The patient’s medication history contained olanzapine 10mg daily and
bupropion SR 150 mg twice daily; the indication for the bupropion was unclear. The patient
admitted to occasional nasal insufflation (amount not quantified), occasionally resulting in
seizures, over the past three years. On the present occasion he denied alcohol or other illicit
drug use. He reported receiving a “cocaine high” from the nasal insufflation of bupropion.

Langguth et al. 2009\(^\text{17}\) reported the case of a 23 year-old female with a history of cocaine use,
depression, and panic attacks. The patient was prescribed bupropion SR 150 mg twice daily for
depression with initial good effect over several months. However, upon investigation of
worsening of symptoms, the patient admitted to an increasing consumption of cocaine. Further
when cocaine was unavailable the patient reported crushing up to eight bupropion SR 150 mg
tablets and insufflating them, from which she reported effects similar to cocaine, but weaker.
The only effect perceived by the patient as an adverse event from this practice was pain in the nose.

Limitations

Trials examining the efficacy of bupropion in the treatment of adults with ADHD have a number of limitations, including small sample size, limited duration, and a lack of data related to functional or quality of life outcomes. Further, patient populations routinely excluded patients with psychiatric comorbidity and recent substance abuse, reducing the generalizability of the studies to the adult ADHD population seen in clinical practice, and potentially even more so to incarcerated adults with ADHD. Further, all identified trials compared bupropion to placebo, rather than other active treatments; the only available evidence comparing bupropion to other active treatments derives from an indirect comparison which may be confounded by differences between patient populations.

Observational studies describing the harms associated with inappropriate bupropion use employed data from poison information centres. It appears that only a small percentage of such reports could be classified as recreational use. Furthermore, it is likely that only a small minority of individuals who use bupropion inappropriately come to the attention of poison control centres. As such, these studies provide numerator data only; without knowledge of the denominator, the frequency of serious adverse events associated with inappropriate use is unclear. Similarly, case reports of adverse events arising from nasal insufflation provide no information regarding the frequency of adverse events from such actions. No studies were identified which compared harms of inappropriate bupropion use to that of other ADHD treatments.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

RCTs examining the efficacy of bupropion in adult ADHD frequently reported no statistically significant differences between bupropion and placebo; however, studies were hampered by small sample sizes. Meta-analyses suggest that bupropion treatment results in greater reductions in ADHD symptoms compared with no treatment; however, bupropion appears to be less effective than short-acting stimulants. Whether the above findings may be generalized to persons with psychiatric comorbidities or substance abuse disorder is unclear. Head-to-head trials of active treatments with sufficient sample size are required to confirm the efficacy of bupropion.

Observational studies of patients presenting to poison control centres reported that seizure was frequently observed among patients with bupropion overdose; death was infrequent, and neurological sequelae were not reported, although this data did not appear to be sought. The incidence of seizure appears to be dose-related. Case reports indicated that seizure has been observed after nasal insufflation of small numbers of crushed tablets. Other than several case-reports, there is little harms information specific to recreational use of bupropion; the intentions behind the bupropion ingestions that led to inclusion in studies conducted with poison control centre data were often unclear. Thus the extent of bupropion toxicity secondary to inappropriate use, and recreational use specifically, remains unknown.

In conclusion, there is limited evidence of the efficacy of bupropion in ADHD especially compared with other established therapies. Harms associated with abuse, including seizures,
have been reported, but death due to inappropriate use is infrequent. The extent to which abuse is a problem in a given institution, as well as the abuse history of individual patients may be important considerations in making treatment decisions.

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REFERENCES:


APPENDIX 1: Summary of Systematic Reviews

Table 1: Systematic Review by Verbeeck et al. 2009<sup>5</sup>

<table>
<thead>
<tr>
<th>Title</th>
<th>Antidepressants in the treatment of adult attention-deficit hyperactivity disorder: a systematic review</th>
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<tbody>
<tr>
<td>Methods</td>
<td>Search: bibliographic databases (Cochrane Library [Central], PubMed, PsycINFO) to August 2008. English language only.</td>
</tr>
</tbody>
</table>
| Requirements for trial inclusion: | Design: controlled trials  
Patients: adults with ADHD  
Intervention: antidepressants (including lithium)  
Comparator: placebo  
Outcomes: not specified |
| Selection/Data extraction: | two reviewers selected studies, however it was unclear if this was independently done, and there was no indication of duplicate data extraction |
| Included studies | 8 RCTs included (N=560, range 30 to 162)  
- Bupropion (5 trials; N=389, range 30-162)  
- Lithium (1 trial; N=32)  
- Paroxetine (1 trial; N=98)  
- Desipramine (1 trial; N=41) |
| Results | **Bupropion versus placebo**  
Based on the pooled analysis of the physician-based clinical global impression of improvement (CGI-I); based on the proportion of patients achieving CGI-I scores of 1 (very much improved) or 2 (much improved) bupropion was determined to be more efficacious than placebo; OR (95% CI) = 2.42 (1.09, 5.36) |
| Author’s Conclusions | The evidence base regarding the use of antidepressants for ADHD is not large. Of the antidepressants examined, only bupropion appears to have at least a medium effect on symptoms, but the effect is less than with stimulant medications. |
| Limitations |  
- Limited literature search (published trials only)  
- Unclear if duplicate data extraction performed  
- Data pooling was restricted to one subjective outcome |

ADHD=attention deficit hyperactivity disorder; CI=confidence interval; OR=odds ratio
Table 2: Systematic Review by Peterson et al. 2008

<table>
<thead>
<tr>
<th>Title</th>
<th>Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: a systematic review and indirect comparison meta-analysis</th>
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<tr>
<td>Methods</td>
<td>Search: bibliographic databases (Cochrane Database of Systematic Reviews and Register of Controlled Trials, Medline, EMBASE, PsycINFO) all to 2007 with the exception of EMBASE which was to 2004. Also, reference lists of included studies (Food and Drug Administration Drugs@FDA) and drug information materials submitted pursuant to a request to manufacturers. English language only. <em>Requirements for trial inclusion</em> Design: RCTs Patients: adults with ADHD Intervention: amphetamines, methylphenidate, dexamethylphenidate, modafinil, atomoxetine, bupropion Comparator: placebo Outcomes: clinical response, change in ADHD symptom scores, sleep or appetite disturbances, anxiety, cardiovascular events, treatment discontinuation <em>Selection/Data extraction:</em> two reviewers independently selected studies and extracted data. Disagreements resolved through consensus.</td>
</tr>
</tbody>
</table>
| Included Studies | 22 RCTs included (N=2203, range 22-280)  
- Bupropion (3 trials; N=261, range 40 to 162)  
- Methylphenidate (11 trials; N=729, range 25 to 149)  
- Amphetamines (4 trials; N=434, range 30-255)  
- Atomoxetine (3 trials; N=558, range 22 to 280)  
- Dexamethylphenidate (1 trial; N=221) |
| Results | **Bupropion versus placebo**  
Based on pooled analysis of clinical response from 3 trials, long acting forms of bupropion were determined to be more efficacious compared with placebo; RR (95% CI) = 1.87 (1.36, 2.58).  
**Short-acting stimulants versus bupropion**  
Based on indirect comparisons of clinical response, short-acting stimulants (8 trials) were determined to be more efficacious compared with long-acting forms of bupropion (3 trials); RRR (95% CI) = 2.24 (1.23, 4.08) |
| Authors Conclusions | Conventional short-acting stimulants (e.g., immediate release methylphenidate) have greater efficacy compared to non-stimulants (e.g., bupropion) for the treatment of ADHD in adults |
| Limitations |  
- Definition of clinical response (pooled outcome) differed between trials  
- Indirect comparison analyses may be confounded by between trial heterogeneity in patient characteristics |

ADHD=attention deficit hyperactivity disorder; CI=confidence interval; N=number; RCT=randomized controlled trial; RR=relative risk; RRR=relative risk ratio