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Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant

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Abstract: Bupropion has been used as an antidepressant for over twenty years, though its licence for such use varies and it is typically a third- or fourth-line agent. It has a unique pharmacology, inhibiting the reuptake of noradrenaline and dopamine, potentially providing pharmacological augmentation to more common antidepressants such as SSRIs. This systematic review and meta-analysis identified 51 studies, dividing into four categories: bupropion as a sole antidepressant, bupropion co-prescribed with another antidepressant, bupropion in 'other' populations (e.g. bipolar depression, elderly populations), and primary evaluation of side effects.

Methodologically more robust trials support bupropion's superiority over placebo, and most head-to-head antidepressant trials showed an equivalent effectiveness, though some of these are hindered by a lack of a placebo arm. Most work on the co-prescribing of bupropion with another antidepressant support an additional effect, though many are open-label trials. Several large multi-medication trials – most notably STAR*D – also support a therapeutic role for bupropion; in general it had a similar effectiveness to other medications, though this literature highlights the generally low response rates in refractory cohorts. Effectiveness has been shown in 'other' populations, though there is an overall dearth of research. Bupropion is generally well tolerated, and it has very low rates of sexual dysfunction, and is more likely to cause weight loss than gain.

Our findings support the use of bupropion as a sole or co-prescribed antidepressant, particularly if weight gain or sexual dysfunction are, or likely to be, significant problems. However there are notable gaps in the literature, including less information on treatment naïve and first presentation depression – particularly when one considers the ever reducing rates of response in more refractory illness. There are some data to support bupropion targeting specific symptoms, but insufficient information to reliably inform prescribing, and it remains uncertain if bupropion pharmacodynamically truly augments other drugs.

Introduction

Major depressive disorders (MDD) are a leading global cause of morbidity (Ferrari et al., 2013; Kessler et al., 2003; Murray et al., 2013) affecting up to a fifth of individuals (Hirschfeld, 2012), four fifths of whom will have multiple illness episodes (Bulloch, Williams, Lavorato, & Patten, 2014).

Guidelines generally advocate Selective Serotonergic Reuptake Inhibitors (SSRIs) as the first-line pharmacological intervention, primarily due to their more benign side-effect profile rather than any superiority in efficacy (NICE, 2009). A so-called “therapeutic trial” of a minimum recognised dose over about six weeks is ordinarily recommended before changing medication, and treatment resistance is usually defined as failure to respond to two such trials. Disappointing data indicate that about half of patients discontinue their treatment during such an initial time frame (Melfi et al., 1998).

Response, typically defined as a $\geq 50\%$ symptom reduction, is typically seen in about half to three quarters on a first trial of an antidepressant, with symptom remission occurring in about a third (Nemeroff et al., 2008; Trivedi, Rush, et al., 2006). Unfortunately many individuals prove resistant to multiple first and second line pharmacological interventions (Coplan, Gopinath, Abdallah, & Berry, 2014; Rush et al., 2004). Treatment options thereafter include changing drug class or adding a second agent, though there are not convincing data to clearly support one strategy over the other (Rush, 2007); the overall literature on pharmacological ‘next-steps’ has numerous options, but most without strong evidence bases (Taylor, Paton, & Kapur, 2015).

Most antidepressants act through increasing the synaptic levels of serotonin and/or noradrenaline (norepinephrine) through various pharmacological mechanisms. Bupropion is an aminoketone, and has a unique pharmacology, inhibiting the reuptake of both noradrenaline and dopamine. It has no effects on serotonin, histamine, acetylcholine, or adrenaline (epinephrine) receptors; it is thus not associated with significant sedation, cognitive or anticholinergic gastrointestinal, or hypotensive side effects (Stahl et al., 2004).

Bupropion has been licensed for depression in the United States since the late 1990s (Fava et al., 2005); an extended formulation version became available in 2007. In the United

Kingdom it is only licensed for the treatment of nicotine addiction, though it is prescribed off-licence for depression. There is literature to supporting its effectiveness as an antidepressant in various populations, and data that it can cause weight loss and help sexual dysfunction. However to date there have been no systematic reviews or meta-analyses of its effectiveness and side effect profile in affective disorders.

Aims

To systematically evaluate and meta-analyse the effectiveness of bupropion as an antidepressant, both when prescribed alone, and in combination with other antidepressants, and its side-effect profile, particularly effects on weight and sexual dysfunction.

Methods

Search Strategy. An electronic search was conducted between March 19, 2015 and March 27, 2015. Potentially relevant studies were identified by searching the following databases: PsycInfo ((1806 – 2015, March 27) / Medline (1946 to 2015, March 27) / Embase (1980 to 2015, March 27)) via OvidSP, PubMed, Web of Science (Core Collection), and The Cochrane Library. The search criteria were as follows: “bupropion” OR “Wellbutrin” OR “Aplenzin” OR “Forfivo” OR “Zyban” OR “Amfebutamone” combined with AND “major depress*” OR “(MDD)” OR “depress*” OR “mood disorder” OR “depressive-disorder” OR “bipolar” OR “unipolar” OR “bipolar affective disorder” OR “seasonal affective disorder”. The review was limited to articles published in English, and a thorough search of grey literature was not undertaken. The reference list of each included study and relevant reviews were examined for potential studies.

Participants. Studies that looked at adult (18-65) and elderly populations (≥ 65), with a diagnosis of Major Depressive Disorder (MDD), Bipolar Affective Disorder, Seasonal Affective Disorder, Dysthymia, or Postnatal (/postpartum) depression (as defined by DSM-V or ICD-10, or previous versions of these diagnostic manuals) were included.

Intervention. Randomised controlled trials (RCTs) and open label trials evaluating the effect of bupropion (any dose or formulation) on depressive symptoms were included.

Comparator intervention. RCTS with a placebo-arm, head-to-head trials with no placebo-arm and augmentation trials were deemed eligible for review.

Outcomes. Only studies evaluating effectiveness through validated measures were included, namely the following: Hamilton Depression Rating Scale (HDRS/HAM-D: (Hamilton, 1960); Montgomery Asberg Depression Rating Scale (MADRS: (Montgomery & Asberg, 1979); Inventory for Depressive Symptomology (IDS: (Rush et al., 1986); Structured Interview Guide for the Hamilton Depression Rating Scale — Seasonal Affective Disorder Version (SIGH—SAD: (Williams, Link, Rosenthal, & Terman, 1988).

Study Design. Only journal articles post 1990 were included for review, with case studies (≤ 3 participants), expert opinions, and poster presentations excluded.

Study Selection. 14372 reports were initially identified (see Figure 1); after adjusting for duplicates (9817), 4555 articles remained. 4417 articles were excluded as unsuitable based on title and abstract. 138 full text articles were evaluated, 87 of which were excluded for being: conference abstracts or presentations, pre-1990 trials, case studies, a non-included patient population, failure to separate results according to treatment or disorder, and for not containing original data. 51 studies ultimately met the criteria for qualitative synthesis, dividing into four major groups: those evaluating bupropion as a sole pharmacological intervention in MDD (n=27); those evaluating its co-prescribing with a second antidepressant in MDD (n=13); the treatment of 'other' populations such as bipolar depression and the elderly (n=11); and primary evaluation of side effects (n=13).

Data Extraction. Data was extracted by two authors (KP and SA). Extracted data concerning patient characteristics and study results are available in Tables 1 and 2. For quantitative analysis, effect sizes were converted to Hedge's g , to decrease the risk of bias associated with standardized mean differences.

Data Analysis. In light of the limited amount of data for quantitative analysis as well as the hypothesis that true effect sizes would differ depending on sample and treatment characteristics, random-effects models were chosen as most appropriate for the meta-analysis. Statistical procedures were carried out using *Stata*⁴⁵, using the *metan* package for the meta-analysis, and the *metafunnel* and *metabias* packages for assessment of publication bias. *P*-values below 0.05 were accepted as being statistically significant.

Results

A) Bupropion monotherapy

27 trials evaluating bupropion in the treatment of MDD were identified, running from 6- to 44- weeks in treatment duration. Of these, 21 trials were double blinded RCTs, of which one had a two phase design (double blinded RCT, followed by open label phase), one was single blinded, and five were open label. Eleven studies compared bupropion with placebo; ten compared to an SSRI (of which five additionally had a placebo arm); four compared to an SNRI (of which two had a placebo arm); and one trial compared bupropion to an SARI, and one to a tricyclic antidepressant (TCA), of which neither had a placebo control. Bupropion was efficacious in reducing depression scores in 24 of the 27 trials, and, where evaluated, showed comparable levels of efficacy to the other classes of antidepressant.

Placebo Trials

Five of the six open-label placebo trials reported a statistically significant clinical improvement in favour of bupropion (Brown, Vornik, Khan, & Rush, 2007; Fava et al., 2003; Ferguson et al., 1994; Gross, Nourse, Wasser, & Bukenya, 2007; Walker et al., 1993), one (Tomarken, Dichter, Freid, Addington, & Shelton, 2004) did not demonstrate between group differences: they are described in Table 2. Of the six double blinded, placebo controlled RCTs, two evaluated flexible dosing of bupropion. In the earlier study (Lineberry et al., 1990)

(n=216) bupropion was titrated to a maximum of 100mg/TID. Intention to treat (ITT) analysis demonstrated significantly greater HAM-D, MADRS, and CGI changes for the bupropion group over six weeks in both observed case analysis ($p<0.05$ for all) and in last-observation-carried-forward (LOCF) analysis ($p<0.01$ for all). 54% attained response ($\geq 50\%$ reduction in HAMD-D total scores) on bupropion, significantly more ($p=0.01$) than the 34% in the placebo group. In the work by Jefferson et al. (2006) (n=270) the majority of patients (59%) received maximum dosage (450mg/d) bupropion (vs 38% on 300mg/d). Clinician reported *response* rates (IDS-C-30) were statistically significant for the bupropion group (50% vs. 35%, $p=0.009$), but self-reported response rates were not (53% vs. 45%, $p=0.084$) at the 8 week endpoint; *remission* rates were significantly greater in both clinician (41% vs 27% respectively, $p=0.01$) and self-reports (32% vs. 18% respectively, $p=0.005$).

Two RCTs evaluated fixed dosing regimens over eight-week timeframes, with contrasting results. In the most recent study (Koshino, Bahk, Sakai, & Kobayashi, 2013) ITT analysis of 564 Japanese and Korean participants (randomised to bupropion 150mg/d, 300mg/d, and placebo in a 1:1:1 ratio) reported no statistical differences between bupropion SR and placebo on MADRS total scores ($p=0.853$), response ($\geq 50\%$ reduction in MADRS) or remission (MADRS ≤ 11) rates, though the authors note the significant changes in their placebo group by the study end that reduced between-group differences. Posthoc analysis showed a trend towards response in those diagnosed with severe MDD. The study had notably stringent inclusion criteria to reduce the potential enrollment of patients with mild depression, a factor reported to impact placebo response rates in clinical trials (Posternak, Zimmerman, Keitner, & Miller, 2002). However, mean MADRS baseline scores (31.8-32.1) did not seem to differ widely with those reported by other authors in this review who used the same measure. Conversely an earlier study of similar design (n=362), Reimherr, Cunningham, Batey, Johnston, & Ascher (1998) reported that bupropion dosed at 150mg/d and 300mg/d significantly reduced HAM-D and CGI-I total scores ($p<0.05$ and $p<0.01$, respectively) compared with placebo. Notably, this study had a lower study completion rate (54%) and, interestingly, of the 46% of patients that had prematurely discontinued, the majority were from the placebo group, with withdrawal due to inadequate response or because their condition had deteriorated.

A two phase trial evaluated the long-term efficacy and weight change (described later) of fixed dose (300mg/d) bupropion. Weihs et al. (2002) administered bupropion dosed at 150-300mg/d in an open label design for eight weeks (phase 1); those who responded were then recruited for a 44 week double blind, placebo controlled randomised fixed dose (300mg/d) study (phase 2). In this study the primary outcome measure was time to relapse, defined as the prescription of new antidepressant or the use of electroconvulsive therapy (ECT), and the study did not report additional data on changes in HAM-D scores. In phase 2 (n=417) of those patients who relapsed, mean HAM-D scores were 21 (SD=4.4, 11-30) and a statistically significant difference in favour of bupropion over placebo was demonstrated when comparing the survival curves for the two treatment groups (p=0.004). In the placebo treatment group median time to relapse was 24 weeks after randomisation compared to 44 weeks for the bupropion treatment group. Furthermore, survival estimates demonstrated that 52% of the placebo group would become depressed by the end of the study compared to 37% of the bupropion treatment group (p=0.004) and that by end of year 1 the odds of placebo group requiring treatment were 1.83 times greater than for those in the bupropion treatment group.

In an inverse two phase design with a much smaller sample (n=16) Tomarken et al. (2004) administered bupropion dosed at 100-300mg/d in an double blinded, placebo controlled randomised design for six weeks (phase 1); at study end point participants from the bupropion group were titrated up to 400mg/d and participants from the placebo group to 300mg/d of medication, in an open label design (phase 2) for a further six weeks. The primary aim of this study was evaluating efficacy of bupropion on specific symptom dimensions of depression (which are discussed later), however, the authors also administered the HAM-D. Both bupropion and placebo demonstrated linear declines on the HAM-D during phase one (p<0.001), though the rate of change was greater for bupropion than placebo (p=0.04). Although declines in mean scores were replicated in phase 2 (p=0.005), no significant differences were observed between groups (p>0.3).

In summary, bupropion demonstrated efficacy compared to placebo in five out of the six RCTs, and all but one of the open label trials, with one of the two fixed dosing studies showing no difference. Study sizes in the RCTs were generally reasonable, with the

exception of the Tomarken et al. (2004) cohort; follow-up periods were generally relatively brief, but consistent with typical antidepressant trials.

A subset of 5 studies reported sufficient data to allow for quantitative analysis using meta-analysis. Meta-analysis for the main effect of bupropion on depression scores as compared to placebo control showed a consistent large effect favouring bupropion (Hedge's $g = 2.02$, $df = 4$, $p < 0.001$, $95\%-CI = 2.93 - 1.11$; Figure 2). However, this analysis also revealed high heterogeneity of study findings ($p = 0.001$, $I^2 = 79.4\%$, $\tau^2 = 0.832$), which is reflected in a large prediction interval (PI = 5.28 - -1.24). Moreover, both Egger's ($p = 0.043$) and Begg's ($p = 0.027$) tests for publication bias produced significant results. Thus, the strength of evidence produced by the present meta-analysis needs to be considered with extreme caution.

Bupropion vs SSRI

Ten RCTs identified evaluated the efficacy of bupropion against an SSRI: one compared with escitalopram (Clayton et al., 2006), five with sertraline (Coleman et al., 1999; Croft et al., 1999; Kavoussi, Se graves, Hughes, Ascher, & Johnston, 1997; Rush et al., 2001; Rush et al., 2006), two with fluoxetine (Coleman et al., 2001; Feighner et al., 1991) and two with paroxetine (Grunebaum et al., 2012; Kennedy et al., 2006) Nine trials employed a double blinded, randomised designs: six of which utilised a double dummy approach, which is a technique for retaining blinding when the two drugs cannot be made to appear identical; all participants thus take two treatments, one of which (depending upon the arm they are in) would be a placebo; and five also had a placebo arm. Trials varied in length from eight to 24 weeks, and number of participants from 74 to 785.

Bupropion vs. Escitalopram

A large ($n=785$) RCT by Clayton et al (2006) randomised participants to receive bupropion XL (300-450mg/d, $n=276$), escitalopram (10-20mg/d, $n=281$) or placebo ($n=273$). A primary measure, reported later, was sexual functioning, but compared with placebo both drugs had

statistically superior response ($p=0.015$ and $p<0.001$, respectively) and remission rates ($p=0.018$ and $p<0.005$, respectively), as measured by the HAM-D, with no difference between the treatment groups. However, separation from placebo was not achieved at the statistical level of 0.05 for bupropion for mean HAM-D total scores in the individual or pooled analysis. This is surprising given a statistically significant response rate was achieved in the pooled analysis for bupropion. The authors attribute this discrepancy to their sample size and large placebo response (53%).

Bupropion vs. Sertraline

Five studies compared bupropion and sertraline, two with placebo arms (Coleman et al., 1999; Croft et al., 1999). Three employed a double blinded, double dummy design (Coleman et al., 1999; Croft et al., 1999; Kavoussi et al., 1997), one a double blinded design (Rush et al., 2001) and one was not blinded (Rush et al., 2006). Trials ranged from eight to 16 weeks and 248 to 583 patients. The most recent RCT (Rush et al., 2001), which is fourteen years old, employed a double blind, randomised parallel design in 248 over a 16 week treatment phase. Mean HAM-D scores reduced for both treatment groups, with high response (bupropion, 66% and sertraline, 74%) and remission (bupropion, 55% and sertraline, 63%) rates reported, with no between-group differences. Interestingly a larger ($n=583$) open label, similar mean dosage, trial by the same group (Rush et al., 2006) recorded significantly lower response rates; however there was a broader inclusion of patients with other comorbid somatic or psychiatric disorders, and it is not clear to what degree these factors might have altered the results. Findings from the RCT are in accord with the earlier, similarly designed ($n=241$) trial by Kavoussi et al (1997). Both groups demonstrated a $\geq 50\%$ improvement in HAM-D scores from week six to study endpoint (week 16), with no statistical between-group difference on the HAM-D, CGI-S or CGI-I. Both groups also demonstrated $\geq 50\%$ study-end improvement in anxiety scores, as measured by the HAM-A. Neither trial had a placebo arm, nor were p values reported.

Two early studies employed more rigorous, and similar, methodological designs. Coleman et al. (1999) reported mean HAM-D scores in the bupropion, sertraline *and* placebo groups improved by $\geq 50\%$ by week 8, but only bupropion was statistically significantly superior to

placebo by this point ($p < 0.05$). Croft et al (1999) reported the same reduction in depression scores by week 8 (from week 6) ($p < 0.05$) LOCF analysis for both active treatment groups, with no statistically significant between them. A statistically significant HAM-D clinical response was observed in bupropion (66%, $p < 0.004$) and sertraline groups (68%, $p = 0.002$) compared to placebo (47%). These two trials, plus work by Reimherr et al (1998) reported that individuals on bupropion showed significantly greater improvement on CGI-S and CGI-I scores. In the Coleman et al (1999) study no difference between sertraline and placebo was established at any time for the CGI-S or CGI-I. Croft et al (1999) reported that although no statistical difference between the groups was observed both treatments were statistically superior to placebo in CGI-S (bupropion, $p = 0.005$ and sertraline, $p = 0.05$) and CGI-I scores ($p < 0.01$).

In summary, all trials that included a placebo arm reported bupropion as being significantly superior to placebo. In the majority of the studies, bupropion and sertraline demonstrated comparable efficacy, with the exception of Coleman et al (1999) cohort where bupropion but not sertraline was superior to placebo.

Bupropion vs Fluoxetine

Two RCTs evaluated bupropion and fluoxetine, with similar study designs including placebo arms. The most recent trial was in 2001 (Coleman et al., 2001); over the 8 week intervention mean HAM-D scores decreased across all groups (total $n = 427$). No statistical difference in response rates was observed between bupropion (56%), fluoxetine (57%) and placebo (50%); however for remission (47%, 40%, 32% respectively), a statistically significant greater rate was seen for bupropion, but not fluoxetine, over placebo ($p < 0.05$). The earlier trial (Feighner et al., 1991) had a smaller sample ($n = 119$) and shorter treatment phase (6 weeks); data similarly demonstrated no statistical difference in HAM-D, CGI-S or CGI-I scores, or response rates (bupropion, 62.5% and fluoxetine, 58.3%), with no statistical difference demonstrated between treatment groups.

Bupropion vs. Paroxetine

Two RCTs compared the efficacy of bupropion with paroxetine, neither utilising a placebo arm. Grunebaum et al (2012) utilised an initial eight week treatment phase (bupropion n=38, paroxetine n=36) in individuals with MDD and elevated suicidal risk factors, followed by a 16 week continuation phase design for those patients who had initially responded to treatment. The primary outcome was suicidal behaviour and ideation, measured on a modified HDRS scores (mHDRS, subtracting suicide item). A reduction in mHDRS scores was reported for both active treatment groups; however for each point more severe at mHDRS baseline, symptoms were 0.46 points lower with paroxetine by week eight. These data suggests that patients with more severe global depression symptoms (minus suicidality) improved modestly more with paroxetine when controlling for suicidal ideation index at baseline. The earlier trial by Kennedy et al (2006) had a larger sample (n=131) and lower mean dosage of medication for both drugs, and reported a statistically significant reduction in HDRS scores for both treatment groups ($p < 0.01$), with no significant differences between bupropion and paroxetine on the HDRS scores, response or remission rates. Overall the lack of a placebo arm hinders the ability to determine either drug's absolute efficacy, though they produced comparable effects in terms of reduction in mean HDRS scores for both treatment groups, with the latest study showing a particular advantage for paroxetine in suicidal patients.

Bupropion vs. SNRIs

Four trials evaluated bupropion and a Selective Norepinephrine Reuptake Inhibitor (SNRI), three of which looked at venlafaxine (Hewett et al., 2009; Hewett, Gee, et al., 2010; Thase et al., 2006) and one duloxetine (Rosso, Rigardetto, Bogetto, & Maina, 2012). The venlafaxine trials were all double blinded, double dummy designs, and two contained a placebo arm; sample size varied from 324–569 subjects and treatment phase from eight to 12 weeks. The single trial evaluating bupropion and duloxetine had a small sample (n=46) and short treatment duration (6 weeks), (Rosso et al., 2012).

Bupropion vs. Venlafaxine

The trial by Hewett et al (n=384) (Hewett et al., 2009) reported a statistically significant difference in mean MADRS total scores for bupropion and venlafaxine compared to the placebo in the LOCF ($p=0.006$ and $p=0.001$, respectively) and observed case analyses ($p=0.003$ and $P<0.001$, respectively), as well as on CGI-I ($p<0.001$ and $p=0.009$), CGI-S ($p=0.003$ and $p<0.001$), and HAM-A ($p=0.019$ and $p<0.001$). A statistically significant greater proportion of bupropion and venlafaxine patients, compared to placebo, met the criteria for response ($p=0.033$ and $p<0.001$, respectively) and remission ($p=0.004$ and $p<0.001$, respectively) at week 8, with no significant differences between the two active treatment groups.

However a larger (n=390) subsequent trial by the same group (Hewett, Gee, et al., 2010) reported no statistical significance in the least squares mean change from baseline MADRS scores, at study endpoint (week 8) for bupropion (180mg/d) compared to placebo. Given the limitations of the studies analysis protocol, no further comparisons at the 0.05 level between active treatment groups and placebo were deemed appropriate, and further results are therefore purely descriptive. Comparison of patients classified as responders or remitters (according to MADRS and CGI-I criteria) were significant for Venlafaxine ($p<0.05$) but not bupropion, and this was also the case for CGI-S and HAM-A scores ($p<0.01$, venlafaxine). In this latter study, Hewett, Gee, et al (2010) argued that the study enrolled a population that was inherently less responsive to bupropion - and more so to venlafaxine - although they recognized that such an argument was speculative.

Thase et al (2006) conducted a randomised, double blind, non-placebo controlled study comparing bupropion and venlafaxine in 324 outpatients with MDD, and reported similar response and remission rates for the bupropion and venlafaxine treatment groups. Although the study reported that a significant difference in favour of bupropion was observed in the LOCF analysis for percentage of patients categorised under remission (for both HAM-D and CGI-I criteria), no p values were provided to further interpret this, and antidepressant efficacy was a secondary aim of the study. In summary bupropion up to doses of 450mg and venlafaxine up to 225mg showed comparable levels of antidepressant activity in two trials. One trial indicated superiority of venlafaxine over bupropion and placebo, however results should be interpreted as descriptive. In some studies mean severity scores were trending

downward at the end of treatment, suggesting there was potential for patients to achieve remission if treatment phases were extended.

Bupropion vs. Duloxetine

One study evaluated the efficacy of bupropion (300mg/d) vs. duloxetine (120mg/d) in a small scale (n=46) six week single blinded, randomised trial in individuals with MDD resistant to SSRIs (Rosso et al., 2012). Rosso et al. reported that both groups demonstrated a statistically significant reduction in mean HAM-D and CGI-S scores at study endpoint ($p < 0.001$), however no differences between treatment groups were found at any time point. Although a similar percentage of patients were categorised as responders (60-70%) and remitters (30-40%), there were no statistical differences between the treatment groups or from baseline to study endpoint (week 6). Whilst the results are positive, given the sample's refractory cohort, and support class change in MDD refractory to SSRIS, interpretation is hindered by the lack of a placebo arm and the small sample size.

Bupropion vs. Trazadone

One study, a RCT, evaluated the relative efficacy of bupropion (225-450mg/d) and trazadone (150-400mg/d), a serotonin antagonist and reuptake inhibitor (SARI) (Weisler et al., 1994). After a one week placebo lead in, 124 outpatients with mild-moderate depression were randomised to one of the two drugs. At the six week follow-up there were no significant differences between the compounds, though trazadone showed earlier gains that might have been due to improved sleep. 58% of bupropion and 46% of trazadone patients were rated as much or very much improved by the end, though the study lacked a placebo arm, and only numerical values of improvement were provided.

Bupropion vs. TCAs

A double blind, double dummy RCT (Masco et al., 1994) evaluated bupropion (n=55) against nortriptyline (n=50) over a six week treatment phase. Improvements on HAM-D scores and response rate (bupropion, 40% vs. nortriptyline, 48%) were comparable across the two treatment groups. As with the trazadone study, there were some early benefits for nortriptyline that the authors considered might be due to a disproportionate weighting of the sleep index on the HAM-D.

B) Bupropion combined with other medication

Thirteen reports evaluated bupropion co-prescribing, with sample sizes from 25 to 565 participants, and trial durations of 4 to 52 weeks: five were RCTs, of which four were double-blinded; seven were open label studies and one was a longitudinal study. Two were part of the STAR*D trial, of which one was a double blinded, randomised trial (Bech, Fava, Trivedi, Wisniewski, & Rush, 2012) and one an open label, randomised trial (Trivedi, Fava, et al., 2006).

Bupropion co-prescribed with SSRIs

Five reports evaluated the efficacy of adding bupropion to SSRIs. A methodologically unique work by Weissman et al (2015) followed the progress of mothers with depression (n=76) randomised to receive bupropion, escitalopram, or their combination over 12 weeks; their children's (n=135) wellbeing was independently assessed. There were no between-group differences for the women, all groups showing statistically significant improvements as measured on the HAM-D ($p < 0.001$); there was an overall remission rate of 67%. However the effect upon their children varied, and depended upon the mothers' baseline symptom profiles; mean Children's Depression Inventory (CDI) scores declined significantly among children whose mothers received escitalopram monotherapy compared with both bupropion monotherapy ($p < 0.04$) and combination treatment of bupropion and escitalopram ($p < 0.001$). Subanalysis of this interesting finding showed that those children

with mothers with a so-called high 'negative affectivity' (which includes the symptoms of guilt, irritability, and fear/anxiety) only improved when their mothers were on escitalopram; mothers in this group reported improvements in their abilities to listen to their children, and the children described the mothers as becoming more caring during treatment. Negative affectivity has been linked with serotonergic dysfunction, which may explain bupropion's lack of impact on this domain.

A single blind RCT (Gulrez, Badyal, Deswal, & Sharma, 2012) evaluated 60 outpatients showing a partial response on SSRIs (escitalopram 10-30mg/day, citalopram 20-60mg/day, paroxetine 25-75mg/day, and sertraline 50-200mg/day; all on treatment 4 weeks). Participants were randomly assigned to have either placebo or bupropion sustained release (150-300mg) added to their antidepressant. By the end of week 4, both groups had significantly improved, but the decrease in depression scores (measured on the HDRS, MADRS and ADI) were significantly greater in those co-prescribed bupropion.

Three open label studies evaluated the addition of bupropion to citalopram or escitalopram, an SSRI that is highly selective for the serotonin reuptake transporter. A novel design naturalistic study by Lam, Hossie, Solomons, & Yatham (2004) explored treatment strategies – whether to augment or switch medication - in 61 individuals taking either citalopram or bupropion SR (at a therapeutic dose but showing minimal improvement) for at least six weeks. Eligible participants, all of whom had failed to respond to at least one previous antidepressant, had, in alternate months, the other medication *added* to their treatment, or were *switched* to the other drug. An advantage of such a methodology is that it attempts to address the issue of whether it is the combination of medications (which could be additive or synergistic) or the novel compound that accounts for any improvement. At six weeks treatment, the combination condition (n=32) was superior to a monotherapy switch (n=29) in terms of clinical change on the SIGH-SAD score ($p<0.04$) and the proportion of participants in remission (28% vs 7%, $p<0.05$). The combination remission rate was low, but with the caveat that it was measured at six weeks' treatment. Leuchter et al. (2008) examined the co-prescribing of citalopram (mean dose 18mg/day) and bupropion sustained release (mean dose 329mg/d) over twelve weeks in 51 medication free outpatients with chronic or recurrent MDD. Participants were commenced on escitalopram 10mg/d, with bupropion sustained release 150mg/d added at week 1; they were eligible for an increase in

either medication by week 4 (and for bupropion also at weeks 6-10) if they failed to show any, or suboptimal, improvement; mean doses by the trial end were 18mg/d and 329mg/d respectively. 62% showed a response to treatment, 50% attained remission (QIDS-C16 \leq 5). Rates of discontinuation due to side effects were low, at 6%. Similarly, Mohann, Eller, Vasar, & Nutt (2009) prescribed 10-20mg/d of escitalopram to 135 participants with MDD in a 12 week trial (those showing \leq 50% decrease in MADRS scores at week 4 being put on the higher dose); non-responders at week 12 were then co-prescribed 150-300mg/d (depending upon response) bupropion for an additional 6 weeks. By the end of twelve weeks 60.7% were responders, 58.5% remitters on citalopram monotherapy; 41 participants –defined as non-responders - entered the co-prescribing phase, and 61.0% attained response, 53.7% remission in the 6 week follow-on. Interestingly, sub-analysis of symptom changes showed that melancholic features of depression were less responsive to escitalopram monotherapy, but that these appeared to respond well to bupropion augmentation.

Overall, with regards to adding bupropion to SSRIs, there was only one double-blinded RCT, though this did not have a placebo group, and was in a specific cohort of depressed mothers. In this study bupropion and bupropion co-prescribing showed results comparable – though not superior to – SSRI prescribing; the data are interesting in terms of the differential outcomes in the children. The data from the single blinded RCT and open label trials support superior efficacy of bupropion, though the sample sizes are modest, and methodologically, open label trials, with their lack of placebo, are open to challenge.

Bupropion co-prescribed with non-SSRIs

Two studies compared the efficacy of bupropion in adjunction with a non-SSRI antidepressant, in both instances a SNRI.

A six-week double blind placebo-controlled RCT (Fornaro et al., 2014) evaluated bupropion SR (150 or 300mg/day) or placebo added to duloxetine (60-120mg/day) in 48 outpatients with MDD (all of whom had failed at least one drug trial) with DSM-IV criteria *atypical* features (which include increased appetite and food consumption, weight gain, hypersomnia and atypical diurnal variation in mood). No statistically significant differences

were seen between groups, with measurements including the Structured Interview Guide for the HAM-D with Atypical Depression Supplement (SIGH-ADS) in addition to the GAF and HAM-D; 26.1% (duloxetine) and 21.7% (placebo) response rates were attained. The authors noted that the presence of a higher number of atypical features, which generally occur in up to a fifth of those with MDD, significantly predicted non-response, as has been demonstrated in other studies, and may have affected their outcomes.

Spier (1998) evaluated the use of adding bupropion to patients with MDD in a private practice clinic already on venlafaxine or an SSRI in an open-label trial assessing symptom relief and management of drug-induced side-effects in monotherapy non-responders (n=15), and responders (n=10) with side-effects, respectively. A numerical reduction in average CGI scores was observed after response to second agent had stabilised, scores reducing from 5.2 (4–7) to 2.2 (1–4). 12 of the 15 monotherapy non-responders showed a response after the addition of bupropion, but only two of the 10 prescribed this to manage medication side-effects showed any amelioration of their problems. The small sample size, and a very heterogeneous population, inevitably means these results should be treated with caution.

Bupropion as part of multiple medication trials

Six studies compared the efficacy of Bupropion in multiple medication trials.

As part of the highly influential STAR*D project, Trivedi et al (2006) randomised (but in an unblinded fashion) 851 individuals with MDD not remitting on citalopram (mean dose 55mg/d, mean duration 11.9 weeks) to additionally receive either bupropion XL (n=565, dose up to 400mg/d) or buspirone (n=286, dose of up to 60mg/d); there was no placebo arm. Both treatments had similar results on the HRSD-17 remission, QIDS-SR-16 remission, and QIDS-SR-16 response; however bupropion had a greater reduction ($p<0.04$) and overall score ($p<0.02$) in QIDS-SR-16 scores, and a lower side-effect drop-out rate ($p<0.009$) by the 12-week study end. Subsequent analysis by the same group (Bech et al., 2012) focused on what the authors termed the 'pharmacopsychometric triangle' in comparing bupropion with buspirone augmentation. Under this model, which composites the domains of

antidepressive activity, side-effects, and quality of life, bupropion was superior in all domains (though not to statistical significance for 'quality of life').

In a double blind RCT Blier et al (2010) randomised 105 medication-free participants with MDD to receive either fluoxetine monotherapy (n=28, dose 20mg/d), or one of three mirtazapine (30mg/d) combination groups: with fluoxetine (20mg/d, n=25); with venlafaxine (225mg/d, n=26); or with bupropion (150mg/d, n=26) over a six week period. Although, similarly to the STAR*D work, there was no placebo group, the monotherapy group allowed for evaluation of the hypothesis that any response or remission might be solely due to having more time on an initial compound. There were no significant differences in inter-group drop-out rates, suggesting that polytherapy was tolerated well, but all the combination groups showed significantly greater HAM-D improvements than fluoxetine monotherapy, producing a number needed to treat (NNT) of 3 to 5 over monotherapy. However the combination protocols did not result in any greater rapidity of response. There were no significant between-combination-group differences on the MADRS or CGI. Discontinuation of any drug in those who had shown a marked response led to a relapse in approximately 40%.

A post-hoc analysis of data from a subgroup of patients enrolled in a large (n=296) 52 week open label multi-centre study (Clayton et al., 2014) evaluated the addition of aripiprazole to either bupropion (n=47) or SSRIs/SNRIs (n=245, data pooled) in individuals with MDD. The primary outcome measurements were the safety and tolerability of these combinations, which are reported elsewhere in this paper. For both groups, LOCF improvements occurred over the course of the one year trial; mean changes of -1.4 points in CGI-S scores occurred in the bupropion group and -1.5 points in the SSRI/SNRI group (observed case n=76). In a six week prospective open label study, DeBattista, Solvason, Poirier, Kendrick, & Schatzberg (2003) examined the efficacy of bupropion XL (150 or 300mg/day) added to 25 participants' existing antidepressants (all with MDD and an inadequate response on their current treatment of ≥ 4 weeks), which included SSRIs (fluoxetine, paroxetine, and sertraline) and the SNRI venlafaxine. A statistically significant reduction in HDRS symptoms was demonstrated by the trial end ($p < 0.001$), with 54% demonstrated a clinical response of $\geq 50\%$ symptom reduction. No between drug differences were noted, though the sample size was very small. Bares et al (2013) compared the efficacy of antidepressant monotherapy

(ADM) with combinational anti-depressant (CAD) treatment in sixty inpatients with treatment resistant depression (TRD) in a randomised six week open label study. After a short initial washout period of a day or two, eligible participants were randomly allocated to either six week ADM or CAD groups, with responders from both entered into a further eight week follow-up protocol. The specific new treatment(s) was/were chosen by clinicians based upon professional judgement of individuals' mental state and past psychiatric histories, excluding medications that had previously failed, or drugs of the same class (with the exception of SSRIs). There were no differences from baseline between ADM and CAD groups as measured by change on MADRS or response rates; whilst bupropion was administered to participants in this study, the total number on this in both groups (and the combination(s) in the CAD group) are not recorded, nor are the other drugs reported.

Interpreting these findings, the methodologically strongest work, by Trivedi et al (2006) and Blier et al (2010) support the addition of bupropion to a range of existing first-line antidepressants. However there is little to delineate treatment options further, and the lack of placebo arms is notable.

C) Other population groups

Older Adults

Three studies evaluated the use of bupropion in older adults (≥ 65 years of age) with MDD. Two were RCTs, evaluating bupropion in comparison to placebo (Hewett, Chrzanowski, et al., 2010) and with paroxetine (Weihs et al., 2000). One naturalistic study investigated the use of both bupropion monotherapy and its combination with SSRIs (Steffens, Doraiswamy, & McQuoid, 2001). Trials ranged from 6-12 weeks with bupropion doses ranging from 100-400mg/d. All three studies showed bupropion to be significantly efficacious.

The most recent double-blind RCT, by Hewett, Chrzanowski, et al (2010) demonstrated efficacy for bupropion XR in comparison to placebo ($p < 0.05$) over ten weeks in a large sample ($n=418$); from baseline the median changes in MADRS total score were -15.0 and -11.0 for bupropion XR and placebo, respectively. Weihs et al (2000) ($n=100$) found significant efficacy for both bupropion SR ($n=48$) and paroxetine ($n=52$) for the treatment of

depression in a double-blinded, double-dummy RCT. Mean HAMD (LOCF) scores were similar at baseline for both treatment groups with a 59% reduction in total score for bupropion SR and a 63% reduction in total score for paroxetine by week 6. LOCF analyses found no significant difference in mean HAMD scores between the two drugs. Secondary analyses of CGI-S, CGI-I and HAM-A scores showed improvement in both treatment groups at week 6. No significant differences were found between treatment groups in mean CGI-S, CGI-I or HAM-A scores.

In the naturalistic trial, Steffens et al (2001) (n=31) investigated the use of bupropion SR or IR monotherapy (n=15) and its combination with an SSRI (n=16), with prescribing based upon clinicians' choices. For bupropion monotherapy, 61% were responders (MADRS<15), with 50% achieving partial (CGI=2) or complete (CGI=1) remission. Bupropion and SSRI combination therapy showed 81.2% response (MADRS<15) with 56.2% showing partial (CGI=2) or complete (CGI=1) remission. Overall, 74.2% were classed as responders (defined as a MADRS<15), with 53.3% achieving a partial (CGI=2) or complete (CGI=1) remission.

The general dearth of research in elderly patient groups makes it difficult to draw firm conclusions. However, of the three included studies identified, all show significant efficacy for the use of bupropion in the treatment of MDD, though only one study was a RCT comparing with placebo, and the other works have notably fewer participants, meaning caution is required in interpretation.

Bipolar Affective Disorder

Although defined by pathological mood elevation, depression (so-called bipolar depression) constitutes the majority of illness burden (Lloyd, Giaroli, Taylor, & Tracy, 2011). Three studies investigated the use of bupropion in this group: one double-blind RCT compared it to the selective α_2 adrenergic antagonist idazoxan (Grossman, Potter, Brown, & Maislin, 1999), a single-blinded RCT compared with the anticonvulsant and mood stabiliser topiramate (McIntyre et al., 2002), and a mixed-design study compared bupropion to sertraline and venlafaxine in combination with mood stabilisers (Post et al., 2006). Trial length varied from 6 to 8 weeks with bupropion doses ranging from 75-450mg/d.

In a small study of 14 individuals with bipolar depression, Grossman et al (1999) found significant reductions in HDRS total score by the end of the 6 week trial for both bupropion and idazoxan. ($t=-3.51$, $df=6$, $p=0.01$, for idazoxan; $t=-3.30$, $df=8$, $p=0.01$, for bupropion). In a slightly larger ($n=36$) and longer trial, McIntyre et al (2002) found significant improvements in HDRS-17 total score from baseline to endpoint for both bupropion SR and topiramate ($p<0.001$). Total mean HDRS-17 score decreased from 20 to 9.5 by endpoint for bupropion and from 20.5 to 10 by week 8 for topiramate. This was also reflected in CGI-I total scores, where a significant reduction was observed for both treatment groups at week 8 ($p<0.005$), with no significant differences between bupropion and topiramate ($t(36)=1/653$, $p=0.092$). The number of patients meeting predetermined criteria for response was significant for both bupropion SR (59%) and topiramate (56%) [$t(17)=2.661$, $p=0.03$ and $t(17)=2.542$, $p=0.04$, respectively], and no significant between group differences were observed [$t(36)=1.754$, $p=0.097$].

Post et al (2006) investigated the use of bupropion, sertraline and venlafaxine for bipolar depression as adjuncts to mood stabiliser treatment with a mixed design of open label ($n=27$) and masked randomisation ($n=147$). Continued medication included lithium ($n=68$), valproate ($n=93$), carbamazepine ($n=16$), lamotrigine ($n=8$), typical antipsychotics ($n=8$) and atypical antipsychotics ($n=30$). Response rates ($\geq 50\%$ improvement in IDS score) were 49% for bupropion, 53% for sertraline and 51% for venlafaxine by the study endpoint (week 10). Remission rates (IDS score <12) were 41%, 36% and 34% respectively. No significant differences were found between treatment groups.

Collectively these studies suggest efficacy of bupropion in the treatment of bipolar depression, although no significant differences were observed between the active comparators. However, interpretation is once again restricted due to the dearth in research within this population and notable methodological issues including a small sample size and absence of a placebo group.

Seasonal Affective Disorder

Three studies evaluated the use of bupropion in seasonal affective disorder (SAD). One prospective study utilised bupropion prophylactically in a double-blinded, randomised design (Modell et al., 2005), and two adopted open label designs (Dilsaver, Qamar, & Del Medico, 1992; Seo et al., 2013). Studies ranged from 5 to 8 weeks in length, with doses of bupropion ranging from 150-400mg/d.

In their large (n=1042) multi-site RCT of individuals with a diagnosis of SAD but currently asymptomatic, Modell et al (2005) randomised participants to receive either bupropion or placebo, and found significant reduction in recurrence rates by the following Spring in the active group. Of the total sample, 16% of patients experienced a recurrence of major depression whilst on Bupropion XL, compared to 28% of patients in the placebo group, with an overall relative risk of 0.56. Bupropion XL was favoured over placebo across all three sites ($\chi^2=3.03$, $df=1$, $p=.081$; $\chi^2=3.62$, $df=1$, $p=.057$; and $\chi^2=14.1$, $df=1$, $p=.001$, respectively) supporting bupropion's use in preventing recurrence of seasonal major depressive episodes.

Both open-label trials demonstrated a significant reduction in depressive symptoms. The more recent work by Seo et al (2013) (n=52) found a significant reduction in SIGH-SAD total score by 53% from baseline (27.6 ± 6.5) to week 8. (12.2 ± 6.3) ($p < 0.001$). The earlier, and considerably smaller (n=15) work by Dilsaver et al (1992) found a significant improvement on HAM-D total score from baseline (18.3 ± 6.9) to study end (3.2 ± 2.2) with an average reduction of 15.2 (SD ± 5.7 ; $t=9.6$, $df = 12$, $p < .0001$); there were also significant reductions of modified HAM-D (mHAM-D) total score from baseline (25.5 ± 6.4) to treatment end (4.1 ± 3.1) with an average reduction of 21.4 (SD ± 5.2 ; $t=15.4$, $df=14$, $p < .0001$).

Although yet to be replicated, (Modell et al (2005) demonstrated the potential prophylactic potential of bupropion in patients with SAD. Open label trials have also demonstrated the efficacy of bupropion in reducing depressive symptomology. However, given the limited number of trials these findings should be considered preliminary.

Dysthymic Disorder

A single open-label study evaluated bupropion SR in the treatment of dysthymic disorder, in an 8 week trial of 21 patients (Hellerstein, Batchelder, Kreditor, & Fedak, 2001). A significant

improvement was shown across all measures of symptomatology ($p < 0.001$); HAM-D scores decreased by 73% from 21.71 (SD=5.57) at baseline to 5.90 (SD=3.60) at week 8 ($p < .001$). Cornell Dysthymia Rating Scale (CDRS) total scores also showed a significant decrease from baseline (36.33, SD=9.85) to week 8 (12.43, SD=7.90) ($P < 0.001$). Although in support of bupropion in the treatment of dysthymia, methodologically sound replication is required to validate these preliminary positive findings.

Postpartum depression

One small ($n=8$) study evaluated bupropion SR in the treatment of postpartum depression in an 8 week trial of open-label design (Nonacs et al., 2005). Overall, patients showed a significant response to Bupropion treatment, with a significant reduction in HAMD, CGI and Kellner depression scores ($p < 0.005$). A significant decrease was shown in HAMD scores by week 4 ($p < 0.05$, Wilcoxon signed-ranks test). Given the small sample and study design, further validation of findings is required in support.

D) Side effects

Weight change

Fourteen studies, involving 8137 participants (duration 6-52 weeks) reported bupropion-related weight changes (see Table 3). Overall, the majority concurred that there was significant weight loss in bupropion treated patients (Coleman et al., 1999; Coleman et al., 2001; Croft et al., 2002; Croft et al., 1999; Jefferson et al., 2006; Reimherr et al., 1998; Settle, Stahl, Batey, Johnston, & Ascher, 1999; Weihs et al., 2002), though some studies reported a small weight increase (Blier et al., 2010; Clayton et al., 2014) or no significant change (Hewett et al., 2009; Hewett, Gee, et al., 2010; Koshino et al., 2013; Thase et al., 2006).

Six double blinded RCTs reported significant weight loss during bupropion treatment, including two long-term (52 week) follow-up studies. In the work by Weihs et al (2002) – the antidepressant efficacy data are reported earlier in this review – there was an initial 8 week

open label phase of 518 participants with recurrent major depression treated with bupropion SR 300mg/day; following this the responders (n= 471) entered a 44 week double blind, placebo controlled phase where they were randomised to continue bupropion or to switch to placebo. At week 52, no fluctuations in weight were found in the placebo group compared with baseline (+0.18kg; SD = 11.0), whereas the bupropion SR group had a mean weight loss of 1.13 kg (SD = 15.8); as noted earlier the bupropion cohort had significant improvements in mood over placebo, and one might otherwise expect more illness-driven weight loss in the more depressed placebo group. Interestingly, one bupropion treated patient discontinued from the study due to weight loss of approximately 7.8 kg or 15.2% of her baseline body weight. In a similarly designed open-label study, Croft et al (2002) reported at a mean 1.4 kg loss by week 8 in the open-label phase; following double-blind randomisation at that point, mean weight changes of -1.15kg were reported for the bupropion group (N=2101) and +0.02kg for the placebo arm (N=213) by week 52.

Five briefer 8-week, multicentre, randomised, double-blind, double-dummy placebo controlled studies (totaling 2957 subjects with MDD), also reported weight decreases with bupropion (Coleman et al., 1999; Coleman et al., 2001; Croft et al., 1999; Reimherr et al., 1998; Settle et al., 1999) across these trials median weight loss ranged from 0.9kg to 1.49kg, compared with losses of 0.5kg on sertraline and 1.49kg fluoxetine, and weight gain of 0.1-0.2kg in a placebo groups. In the studies by Reimherr et al (1998) and Settle et al (1999), weight loss was dose dependent, with larger mean decreases on higher dosing regimens.

Four double-blind RCTs reported minimal weight changes over 8 to 12 weeks of bupropion treatment (n=2070), though only the work by Koshino et al (2013) reported statistical comparisons; they found no significant differences in weight change in a cohort of 569 depressed Asian subjects treated with bupropion 150mg/d, 300mg/d or placebo. Thase et al (2006) found a mean weight decrease in the bupropion XL group of 0.1 kg compared with a gain of 0.1kg in the venlafaxine XR group. Hewett et al (2009) and Hewett, Gee, et al (2010) described minimal 8-week weight changes for bupropion, venlafaxine, and placebo groups.

Two studies (n=358) reported mean weight gains associated with bupropion treatment, though these were studies where it was co-administered with another antidepressant. Blier et al (2010) (n=66) reported significant mean weight increases in the bupropion plus

mirtazapine (M=2.7 kg, SD=2.4), venlafaxine plus mirtazapine (M=2.2 kg, SD=2.5) and fluoxetine plus mirtazapine groups (M=3.1 kg, SD=2.5) as compared to fluoxetine monotherapy ($p < 0.001$). In a 52-week open label study ($n= 292$) by Clayton et al (2014) found mean weight gains of +3.1 kg for bupropion plus aripiprazole, and +2.4 kg for an SSRI/SNRI plus aripiprazole.

Sexual functioning

Eleven studies (total participant $n=5582$) measured effect of bupropion on sexual functioning in patients with MDD (see Table 3). The majority divided sexual dysfunction into sexual desire disorder, sexual arousal disorder and orgasm dysfunction, while one study reported sexual functioning as using a single measure. The consensus across the literature was that bupropion did not differ significantly from placebo in *causing* sexual dysfunction; whilst it improved sexual functioning in patients experiencing SSRI-induced sexual dysfunction.

Regarding *causing* sexual dysfunction, Croft et al (1999) and Coleman et al (1999) both reported that significantly more patients treated with sertraline experienced orgasmic dysfunction than subjects treated with bupropion SR or placebo, with an onset of orgasm dysfunction occurred as early as day seven in up to a sixth of those on sertraline. Following a 16 week randomized clinical trial ($N= 248$), Segraves et al (2000) reported that compared to bupropion, more patients in the sertraline group experienced sexual desire disorder (63% of men and 41% of women) and sexual arousal disorder (19% in men, $p=0.02$; 12% in women, $p=0.05$); bupropion treatment was related with an increase in sexual satisfaction (from 57% to 79%). Clayton et al (2006) combined data from two double-blind, placebo-controlled RCTs comparing bupropion ($N=276$) to escitalopram ($N=281$) on measures of sexual functioning. They found, in both the individual studies and the pooled dataset, the incidence of orgasm dysfunction and the incidence of worsened sexual functioning at the end of the treatment (week 8) were statistically significantly lower with bupropion and placebo than with escitalopram ($p<0.05$), and not statistically different between bupropion and placebo. Similarly, Hewett et al (2010) reported no significant difference between bupropion patients and placebo on the Changes in Sexual Functioning Questionnaire (CSFQ), while venlafaxine

treated subjects experienced significant decreases on arousal and orgasm subscales ($p < 0.05$) in an 8 week double-blind, placebo-controlled RCT ($N = 591$). A double blind, double dummy RCT (Coleman et al., 2001) compared bupropion to fluoxetine. The overall incidence of sexual desire disorder significantly decreased only in the bupropion group by the week 8 endpoint ($p < 0.05$). Sexual arousal disorder occurred in significantly more fluoxetine than bupropion or placebo treated patients ($p < 0.05$), with no difference between bupropion and placebo at any point. The incidence of orgasm dysfunction in those on fluoxetine 20mg/d was >2 times higher than that in those on bupropion 300mg/d, and, interestingly, three times higher than that of those on bupropion 400mg/d. Subjectively, more patients in the bupropion group were satisfied with their sexual functioning than in the placebo or fluoxetine groups.

The important issue of potential gender differences in sexual functioning was taken into account by two randomised, double blind trials (Kennedy et al., 2006; Thase et al., 2006), (total $n = 473$ subjects with MDD but without sexual dysfunction). Thase et al (2006) reported that for men, there was a statistically significant difference in sexual functioning in favor of bupropion XL for all comparisons with venlafaxine ($p \leq 0.048$); for women, this was also true at week 5, week 6, and for the average across weeks 5 to 12 ($p \leq 0.043$). Notably, bupropion XL was also superior to venlafaxine XR on the CSFQ subscales for pleasure, desire/frequency, desire/interest, arousal, and orgasm throughout the study period. Following an 8-week treatment period with either bupropion or paroxetine, Kennedy et al (2006) found that women ($n = 68$) in the bupropion group experience significantly higher levels of sexual functioning Sexual Functioning (Sex FX) total, $p < 0.01$; desire, $p < 0.01$; arousal, $p < 0.01$; overall satisfaction, $p < 0.01$). In men ($n = 73$), the analysis revealed a significant treatment effect by visit for Sex FX total ($p < 0.001$), desire ($p < 0.001$), and overall satisfaction ($p < 0.01$). The effect was due to a significant decrease in sexual functioning during paroxetine treatment (Sex FX total, $p < 0.002$; Desire, $p < 0.005$; Arousal, $p < 0.005$; and overall satisfaction $p < 0.057$); at week 8 the paroxetine groups displayed a significant deterioration from baseline, on Sex FX total ($p < 0.01$), desire ($p < 0.01$), arousal ($p < 0.05$), orgasm ($p < 0.01$), and overall satisfaction ($p < 0.01$) scores, whereas no significant change was observed in any of these measures across visits in men randomised to the bupropion SR group.

Several studies evaluated bupropion's effectiveness at reducing *existing* sexual dysfunction: four studies measured changes in sexual functioning when subjects were either switched from their previous SSRI/SNRI to bupropion monotherapy or bupropion was added to their current SSRI treatment plan. Clayton, McGarvey, Abouesh, & Pinkerton (2001) reported significant improvements in global CSFQ scores by week 2 in the co-prescribing group (SSRI/SNRI+bupropion) and from week 2 to 4 in the monotherapy group (discontinuation from SSRI/SNRI to bupropion monotherapy), with gains over baseline maintained by the 8-week endpoint ($p < 0.05$). A similar pattern was observed on the subscales of sexual desire and orgasm, mean scores differing significantly ($p < 0.05$) from baseline to weeks 4 and 8, indicating improvement following SSRI discontinuation and the start of bupropion monotherapy, but not for co-prescribing. In a later, placebo controlled, double blinded study ($n=42$) by the same group Clayton et al (2004) reported that neither the addition of bupropion nor placebo produced a change in CSFQ total scores after 4 weeks; however, those co-prescribed bupropion self-reported improved desire and frequency of sexual activity (Wilk's $F = 5.47$, $df = 1$, $p = .024$). Dobkin et al (2006) conducted a 10 week open-label study of 18 ethnic minority depressed women with poor response to current SSRI treatment and hypoactive sexual desire. Compared to baseline measurement, after 8 weeks of bupropion monotherapy (i.e. week 10), there were significant improvements in desire [$F(1,17)=34.86$, $p < 0.001$], arousal [$F(1,17)=25.99$, $p < 0.001$], and orgasm [$F(1,17)=20.16$, $p < 0.001$]. Post-hoc analyses indicated that improvements were observed as early as week 2 (end of cross-taper) for desire scores [$t_{17}=3.94$, $p=0.001$], and at week 4 for arousal ($t_{17}=5.62$, $p < 0.001$) and orgasm scores ($t_{17} = 4.53$, $p < 0.001$). More recently, a 12 week double blind RCT of 218 women with SSRI-induced sexual dysfunction reported the Female Sexual Function Index total score was higher in the bupropion sustained release group (25.9 (5.12), 95% confidence interval (CI) 22.2–29.4) than in those randomised to placebo co-prescribing (17.2 (4.9), 95% CI 15.8–20.1) ($p = 0.001$). In addition, at the end of the trial the mean (SD) scores for desire (4.1 (0.7), 95% CI 3.5–4.8; $p = 0.001$), arousal (4.4 (0.6), 95% CI 3.7–4.8) ($p = 0.01$), lubrication (4.4 (0.4), 95% CI 3.3–4.8) ($p = 0.001$), orgasm (4.4 (0.5), 95% CI 3.7–4.7) ($p = 0.001$), and satisfaction (4.2 (0.7), 95% CI 3.4–4.8) ($p = 0.001$) were significantly higher in the bupropion group (Safarinejad, 2011).

Other side-effects

The majority of identified studies described side effects frequently reported (generally defined as occurring at least 5% of patients). Overall, following bupropion treatment, side effects experienced were generally of mild to moderate intensity, and the most commonly reported were: dry mouth (5% - 34.5%), insomnia (1% - 27.8%), headache (3% - 34%), and nausea (7% - 21%). Other adverse events occurring seldom in the literature included restlessness, anxiety, constipation, dizziness, nasopharyngitis, and fatigue. Discontinuation rates due to adverse events ranged from none to 55%, however, bupropion was not significantly different from other antidepressants and in some cases placebo treatments.

Discussion

This review set out to systematically evaluate and meta-analyse the existing evidence for the use of bupropion as an antidepressant. 51 studies were identified, clustering into four groups: the sole use of bupropion; bupropion co-prescribing; 'other' populations; and side effects. Regarding the methodologically more robust data, bupropion showed superiority to placebo in most, but not all RCTs; study sizes were generally reasonable, encompassing several hundred participants, though follow-up times were typically relatively brief, lasting in the range of eight weeks or so. **Meta-analysis of trials where sufficient data were provided to allow sufficient extraction, produced a result further supporting bupropion in this group; however the small number of trials so included means that caution should be exerted in interpreting this.** Comparator trials generally showed bupropion as having equivalent effectiveness to other antidepressants, but a considerable number of studies did not have placebo arms, most drugs had few trials (sertraline 5; fluoxetine 2; paroxetine 2; venlafaxine 3; and one each for escitalopram, duloxetine, trazadone and nortriptyline); furthermore many of the studies are now of considerable age. The RCT by Clayton et al (2006) is notable both for its large size (n=785) and its inclusion of a placebo arm in addition to bupropion and placebo; however whilst the pooled active drug data were superior to placebo, analysis of bupropion alone failed to show separation from placebo. The most evaluated head-to-head drug was sertraline, and all trials with placebo arms showed bupropion's superiority to placebo, and equivalence with the comparator drug.

Bupropion, arguably, has had a greater role in clinical practice as a co-prescribed antidepressant; this may be due to several factors including (in some jurisdictions) limited or lack of licensing, a lack of clear evidence or recommendations as a first line drug, and the fact that its pharmacodynamics would suggest it might augment existing first line medications. This latter factor would appear to be borne out in the studies adding bupropion to the highly serotonergic drug (es)citalopram. Data from these trials are supportive of bupropion co-prescribing, with the caveat that most were open-label. Results from co-prescribing with non-SSRIs are sparse, with a single trial of duloxetine and one of venlafaxine: the former had disappointing results, whilst the latter is again marked by an open label methodology. It is perhaps the multi-medication trials that have most raised bupropion in clinicians' awareness, notably the STAR*D work that has been widely reported. STAR*D supports the addition of bupropion as an intervention of value, but with the caveats that overall outcomes in TRD are disappointing, and numbers going into remission are low in all secondary treatment arms. The study emphasises the variation and difficulty in predicting individuals' responses. The work by Blier et al (2010) is consistent with this, albeit in a trial with far fewer participants. Both of these support the principle of co-prescribing, but highlight that bupropion, whilst a reasonable option, is not superior to other drug choices.

Data from the 'other' section are interesting, but generally marked by a dearth of research. Positive results were seen in bipolar depression, older adults, seasonal affective disorder, a dysthymia, but considerable caution is required in interpretation due to the general lack of studies in this area. Of this section the work by Modell et al (2005) on SAD is noteworthy due to its large size (n=1042), randomised nature, and the fact it was undertaken prophylactically in asymptomatic individuals. Their results support the prophylactic prescribing of bupropion in SAD, though the absolute numbers of those relapsing were low in both groups, which raises the issue of benefit:risk ratios in prescribing medications.

With regards to side effects, bupropion is generally a well-tolerated drug, the type, severity, and frequency of problems fitting with that of most SSRIs. There are two clear notable differences however; weight change and sexual functioning. The evidence is in favour of bupropion producing no weight gain, and typically weight loss, and that it can improve

sexual functioning in depressed individuals. This is potentially very important, as these are considerable drug and illness induced difficulties for many with MDD.

Interpreting this broad literature, several challenges emerge. As has been mentioned, the methodology of many studies can be questioned; there were many open-label trials, and many of the head-to-head and multi-drug studies did not have placebo arms. Inevitably cross-comparison between different head-to-head drugs is difficult, not least as some drugs have single trials, some of which are almost twenty years old. Follow-up periods were typically brief, in the order of a couple of months or so. However, in general where response to an antidepressant occurs, it tends to be within such a timeframe (Fornaro et al., 2014).

Regarding participants, there was a wide range of inclusion and exclusion criteria, not least in defining (or not defining) if individuals were treatment refractory, and indeed no clear consensus on what that meant. This factor is critically important if one considers that one of the major outcomes of STAR*D was showing how poor responses are in general as one moves through sequential stages of depression management. As such, much bupropion prescribing is thus potentially in individuals fundamentally more refractory to pharmacological intervention, but the variation in study criteria makes this very difficult to elucidate as a factor; work on first episode and treatment naïve individuals would be welcomed.

Zimmerman et al (2004) reported that the targeting of specific symptoms and the desire to avoid certain side effects were the most frequently given reasons expressed by a small US sample (n=10) of psychiatrists for choosing bupropion, namely hypersomnia, hyperphagia and fatigue; high levels of anxiety, irritability, poor sleep and appetite were significantly less often cited as a reason for prescribing. For approximately half of the patients, the desire to avoid weight gain or sexual dysfunction was reported as a reason for choosing bupropion. The issue of bupropion's novel pharmacology is also one of the primary reasons behind many of co-prescribing studies, with the consideration that its differing mechanism of action might compliment – or enhance – another drug. This is a complex and incompletely understood area, and there are several possibilities, none yet clearly proven. The first is a potential pharmacokinetic effect wherein co-prescribing will change the plasma protein binding and availability of the drugs; thus additional effects might arise solely through an

effective increase in the unbound and active level of one or other – or both – drugs. A second possibility is that there is a pharmacodynamic additive effect through the use of two compounds, each producing different pharmacological effects. Finally it is further possible that there is a synergistic effect, with the combined compounds pharmaco-kinetically and/or -dynamically producing an effect greater than the sum of their individual actions. Problematically, there are few RCTs, and fewer of sufficient size or duration, that might allow elucidation of these factors; an issue compounded by the earlier mentioned variable population responses. It is just as possible in open label work that the effective factor is *time*; a second drug is added, and a response is seen, but this is, in fact, just a delayed response to the first compound.

Following on from this, depressive disorders are becoming ever more to be seen as fundamentally heterogeneous conditions with as yet incompletely understood but highly complex pathway disorders involving numerous gene and environmental interactions (Koutsouleris et al., 2015). In psychosis studies there has been an argument to reconceptualise ‘the schizophrenias’ (Arnedo et al., 2015), and we would argue that ‘the depressions’ are equally likely. As such, the bupropion data face a similar problem to that of the wider pharmacological literature; the critical question – that does not have an answer at this time – *in whom* and *when* might bupropion work, rather than the typical cruder class-effect query of “is it effective in depression?” This is of particular interest with bupropion given its differing mechanism of action that is primarily noradrenergic and dopaminergic (but no serotonergic) effects, raising the interesting question about whether it might target specific symptoms in depression, or certain types of depression.

With specific consideration of the bupropion literature, there are some interesting findings in this regard, though the field is nascent. The study by Weissman et al (2015), in depressed mothers, is a thought-provoking example. Whilst bupropion was as effective as escitalopram, it was less effective with regards to their children’s mental health; subanalyses showed that escitalopram was more effective with regards to treating ‘negative affectivity’ (guilt, irritability, fear/anxiety), which the authors posit has a more serotonergic underpinning. Another domain specific negative finding was the work by Grunebaum et al (2012) which found bupropion less effective at managing suicidal feelings than paroxetine; this may fit with a literature suggesting that serotonergic dysfunctioning is associated with

suicidality. Fornaro et al (2014) intentionally co-prescribed bupropion with duloxetine in a cohort with atypical depression (carbohydrate craving, hypersomnia etc.) on the basis that bupropion's additional dopaminergic and noradrenergic functioning might provide additional therapeutic gains, though this was not borne out in the (relatively small) sample. Conversely, Mohan et al (2009), in their study of bupropion co-prescribing with escitalopram, showed that so-called 'melancholic features' of depression were more effectively treated by bupropion.

Of the studies that have explored the possibility of bupropion producing a more distinct pattern of changes across specific symptom dimensions, differential response to bupropion has been identified with regards to negative affect. One study reported in this review in the context of HAM-D scores, also used a dimensional assessment of mood based on the tripartite model of mood disorders (Clark & Watson, 1991) administering the mood and anxiety symptom questionnaire (MASQ AD Scale) (Tomarken et al., 2004). The authors reported that bupropion exerted a more robust effect on the positive affect dimension (energy, motivation, enjoyment) but not negative affect (general distress and somatic anxiety). Interestingly, during the earlier phase when bupropion was dosed at a lower range (100-300mg/d) a stronger effect was observed on the affectively negative dimensions, but later within the open label phase where bupropion was dosed at higher range (300-400mg/d) a notably higher effect was observed on the affectively positive dimensions, perhaps suggesting a dose dependant relationship or due to a longer time in treatment. In a closer examination of the effects of bupropion on negative affect, through a post hoc analysis of monotherapy treatment (bupropion vs. escitalopram) in patients with MDD (n=163), Gerra et al (2014) reported that whilst response to escitalopram did not differ significantly between low- and high- negative affect patients, bupropion was significantly more effective for patients with low negative affect than high negative affect ($p < 0.03$). Conversely, escitalopram was significantly more effective than bupropion for high negative affect patients ($p = 0.017$). This suggests that bupropion may be more suitable in the treatment of the core components of depression rather than for the commonly encountered illness-associated anxiety.

The issue of bupropion's lack of a licence is problematic in some jurisdictions, including the United Kingdom. The existing evidence would support bupropion's addition to the

pharmacological armamentarium; however the burdens of obtaining a European licence are bureaucratically and financially considerable. For a pharmaceutical company, this may present an unappealing prospect; having gone through this process, it is likely to be some time before guidelines or local policies promote bupropion, at such point probably recommending it as a third, fourth, fifth (or worse) choice of drug. The head-to-head data do not suggest it should have a higher role than this, but it means that financial returns are likely to be scant in an already bloated market-place, acting as a further disincentive to obtain a licence to market this medication. However, this presents clinicians with a problem; whilst most research shows rough equivalence between various antidepressants, undoubtedly individual responses vary considerably, and there are, and will be, patients who will respond well to bupropion, perhaps better than to other compounds. Of course a current scientific frustration – by no means limited to bupropion – is prospectively identifying such individuals, but the field of pharmacogenomics remains in its infancy, with disappointing results thus far (Penn & Tracy, 2012). However, the lack of a licence means that many clinicians (and potentially patients) will be hesitant to try the drug, and may face further problems such as having difficulties having such prescriptions continued in primary care.

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