Drug and Alcohol Dependence 102 (2009) 116–122

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

A proof of concept randomised placebo controlled factorial trial to examine the efficacy of St John's wort for smoking cessation and chromium to prevent weight gain on smoking cessation

Amanda Parsons[a,*], Jackie Ingram[a], Jennie Inglis[a], Paul Aveyard[a], Elaine Johnstone[b], Karen Brown[c], Mike Franklin[d], Isabel Bermudez[d]

[a] Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[b] Department of Clinical Pharmacology, Old Road Campus Research Building, University of Oxford Old Road Campus, Roosevelt Drive, Oxford OX3 7DQ, UK
[c] Clinical Trial Service Unit, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK
[d] School of Life Sciences, Oxford Brookes University, Gipsy Lane, Headington, Oxford OX3 0BP, UK

ARTICLE INFO

Article history:
Received 28 October 2008
Received in revised form 10 February 2009
Accepted 11 February 2009
Available online 27 March 2009

Keywords:
Smoking cessation
RCT
Antidepressants
Weight gain
Food supplements

ABSTRACT

Background: St John's wort is an effective antidepressant that can reduce tobacco withdrawal symptoms, but it is not known whether it assists cessation. Chromium assists weight loss and might limit post cessation weight gain.
Methods: In a factorial design, we randomised smokers stopping smoking to 900 mg St John's wort (SJW) active or placebo and also randomised them to 400 μm chromium or placebo daily. Treatment started 2 weeks prior to quit day and continued for 14 weeks. Participants and researchers were blind to treatment allocation. All participants received weekly behavioural support. The primary endpoints were biochemically confirmed prolonged abstinence and mean weight gain in abstinent smokers 4 weeks after quitting.
Results: 6/71 (8.5%) participants on active SJW and 9/72 (12.5%) on placebo achieved prolonged abstinence at 4 weeks, an odds ratio (OR) (95% confidence interval) of 0.65 (0.22–1.92). At 6 months, 3 (4.2%) SJW active and 6 (8.3%) SJW placebo participants were still abstinent, an OR of 0.49 (0.12–2.02). Among these participants, the mean difference in weight gain between active chromium and placebo was −0.81 kg (−3.79 to 2.18) at 4 weeks and −3.88 kg (−12.13 to 4.38) at 6 months.
Conclusions: Taking together the absolute quit rates, the small difference between active and placebo, and lack of effects on withdrawal shows that SJW is ineffective for smoking cessation. Insufficient people stopped smoking to properly test the efficacy of chromium in preventing weight gain, but the point estimate indicates a potentially worthwhile benefit.

1. Introduction

The UK is the only country with a widespread network of smoking cessation clinics and also reimburses smoking cessation pharmacotherapy. Despite this, more people buy nicotine replacement therapy (NRT) over the counter than obtain it free or at a much reduced cost from the National Health Service (NHS) (West, 2006). Over the counter medication therefore contributes greatly to public health and it would be valuable to find other pharmacotherapy available without prescription that assists smoking cessation.

One possible smoking cessation pharmacotherapy that is available without prescription is St John's wort (SJW). St John's wort (SJW) is a plant extract that is equally effective with conventional pharmacotherapies in the treatment of depression, whilst causing fewer side effects (Linde et al., 2008). Some antidepressants, including bupropion and nortriptyline, have been proved effective treatments for smoking cessation (Hughes et al., 2007) and it is therefore possible that SJW's antidepressant properties also make it effective in increasing abstinence. One feature common to antidepressants and other pharmacotherapies for smoking cessation is that they reduce urges to smoke and tobacco withdrawal symptoms. There is evidence that SJW reduces urges to smoke and withdrawal symptoms in humans (Becker and Bock, 2003) and signs of withdrawal in mice (Catania et al., 2003), and stimulates dopaminergic neurones similar to bupropion (Franklin et al., 1999), and therefore it may also aid cessation (Uzbay, 2008). However,

* Corresponding author at: Department of Primary Care and General Practice, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
Tel.: +44 121 414 8611.
E-mail address: a.c.parsons@bham.ac.uk (A. Parsons).

0376-8716/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2009.02.006

selective serotonin inhibitors (SSRIs) reduce urges and withdrawal (Covey et al., 2002), but do not increase abstinence rates (Hughes et al., 2007). It is therefore important to test if SJW is able to increase abstinence rates as well as reduce withdrawal.

Two uncontrolled trials have evaluated the effect of SJW in smoking cessation. In one, 24 participants took 900 mg daily of SJW for 1 week prior to and 12 weeks after quit day and 54% were continuously abstinent at 4 weeks and 38% at 12 weeks; abstinence rates that imply possible effectiveness (Lawvere et al., 2006). In Barnes et al. (2006), 28 participants were randomised to 300 mg or 600 mg from 1 week prior to quit day for 12 weeks. Continuous abstinence rates at 4, 12, and 26 weeks were 21%, 18%, and 0%. Thus the data on the efficacy of SJW are mixed and imprecise. We tested SJW as an aid to cessation in the first proof of concept randomised controlled trial. Proofs of concept trials have short-term outcomes, but if no short-term benefit is observed, then efficacy can be excluded (Hughes et al., 2003).

About 80% of smokers gain weight on cessation, on average about 5 kg during the first year (Froom et al., 1998). Chromium (CR), a necessary constituent of diet, has been used to assist weight loss (Vincent, 2003) and as an adjunct treatment in diabetes (Guerrero-Romero and Rodriguez-Moran, 2005). A meta-analysis of trials found that CR supplements led to weight loss of approximately 1 kg, but this result depended upon one trial (Pittler et al., 2003). There is some suggestion that smokers may benefit from additional CR (Guerrero-Romero and Rodriguez-Moran, 2005; McCarty, 2005). In a speculative hypothesis, we also randomised participants to CR supplements or placebo to examine the effect on weight gain in successful quitters.

2. Methods

We gained permission for the study from all appropriate regulatory bodies.

2.1. Participants

Smokers were recruited through advertisement either by direct mail from their general practitioner or from a stop smoking service, or by advertisements in newspapers. Participants were booked into smoking cessation clinics run by the research team. People were eligible if they were aged 18 years and above, smoked at least 10 cigarettes per day and were willing to set a quit date 2 weeks from their first appointment. SJW interacts with medications metabolised by cytochrome P450 enzyme CYP3A4 (Zhou et al., 2004) because SJW is a potent inducer. People on these medications were excluded, as were breastfeeding or pregnant women. We also excluded patients with a history of an eating disorder, severe mental illness, those who regularly used illegal drugs or suffered from alcohol dependence within the past 6 months. People were excluded if they were currently depressed or taking antidepressant medication.

2.2. Randomisation

An independent statistician prepared an excel spreadsheet using Stata to generate two lists of randomly sequenced blocks of 2, 4, or 6, which were passed to the medication packing company. These lists were used to package together medication of SJW or placebo and CR or placebo, which were allocated in sequence to participants in clinic. Participants, therapists, and outcome assessors were blind to the treatment allocation.

2.3. Intervention

Participants were randomised to one of four groups: SJW active CR active (SJWa-CRa), SJW active CR placebo (SJWa-CRp), SJW placebo CR active (SJWp-CRa) or SJW placebo CR placebo (SJWp-CRp). Participants attended seven weekly clinics run by the research team, with quit day coinciding with the third visit. The researchers were trained and provided individual behavioural support to all participants based on withdrawal orientated therapy (Hajek, 1989). Participants commenced SJW/placebo on the second day of the study at a dose of 300 mg three times per day. This dose was chosen because this is the standard dose of SJW for depression (Linde et al., 2008) which has evidence of efficacy (Fava et al., 2005; Szegedi et al., 2005) and we used the Jarsin preparation (LI 160, Lichtwer Pharma, Berlin, Germany), which is a licensed prescription medication in Germany. The Hypericum extract was standardized to between 0.12% and 0.28% hypericin, and the entire study supply came from one batch. Participants began a 400 μm chromium/placebo capsule daily on the second day. Chromium polynicotinate was supplied by Vega Nutritionals Ltd., Walton-on-Thames, Surrey. The dose was similar to that used in a trial of chromium as an antidepressant that led to changes in weight (Davidson et al., 2003) and is 25-fold less than the safe daily maximum intake recommended by the UK Food Standards Agency. Both preparations were dispensed every 2 weeks during the clinical phase of the study (from 2 weeks preceding the quit day to 4 weeks post quit). Participants still quit or attempting to quit at 4 weeks post quit were dispensed a further 8 weeks of medication, receiving 14 weeks in total.

2.4. Measurements

We collected standard smoking and demographic baseline measures at the first visit. At each clinic visit, we recorded tobacco withdrawal symptoms and urges to smoke using the Mood and Physical Symptoms Scale (MPSS) (West and Hajek, 2004) using symptom checklists. We asked participants about adherence to medication, serious side effects, smoking in the past week, and weighed participants. Weight and percentage body fat were measured using a Tanita TBF300MA body composition analyser.

The primary outcome measure for SJW was prolonged abstinence at 4 weeks after quit day measured according to the Russell standard (West et al., 2005). This means that a grace period for the first 2 weeks after quit day was allowed in which slips did not invalidate abstinence and abstinence was confirmed by exhaled carbon monoxide (CO) concentration of less than 10 parts per million (ppm). Those lost to follow-up were counted as smokers and therefore included in the primary and secondary outcome analyses of effect on smoking as treatment failures.

The primary outcome for CR was change in weight baseline to 4 weeks after quit day in participants achieving prolonged abstinence. Baseline weight was defined as the mean of the two pre-quit weights measured at the baseline visit and 1 week later. The mean was used to give a better measure of pre-quit weight less sensitive to fluctuations.

Secondary outcome measures were prolonged abstinence at end of treatment (3 months) and 6 months after quit day, weight gain at 6 months and fat gain in kilogram at 4 weeks and 6 months after quit day. We also report point prevalence abstinence, effects on tobacco withdrawal symptoms, serious adverse events at any time within the study as defined in Good Clinical Practice (2008), and side effects in the first 4 weeks after quit day. The MPSS measures urge to smoke frequency and severity (summed to MPSS-C score), mood changes (summed to MPSS-M score), and some physical symptoms (constipation, sores in the mouth, and cough or sore throat summed to the MPSS-P score) that have been linked to tobacco withdrawal (Hughes, 2007).

It is important to note that we asked participants to continue using medication and attending clinic up to the point that they abandoned their quit attempt. Once they decided it had failed, we no longer dispensed medication nor asked them to attend clinic. The trial took place in a country that offers free effective treatment to smokers wanting to quit, so that treatment failures who wanted to continue to quit were offered standard NHS treatment and referred to an NHS clinic. Even if such participants subsequently quit, they were retained in our analysis as smokers or treatment failures.

2.5. Statistical methods

To calculate sample size for SJW we set the type 1 error rate at 10% and power was set at 80%. We assumed that the quit rate in the placebo group would be 30% (about half the rate achieved by NHS clinics that use NRT and behavioural support). We calculated that 72 patients would be needed to commence therapy with SJW and placebo respectively to detect an increase in quit rate to 50%. This represented a rate ratio of 1.66, less than that observed with bupropion or nortriptyline, which are established effective antidepressants for smoking cessation (Hughes et al., 2007). For weight gain, the mean weight gain when quitting on NRT is 0.3 kg/week, with a standard deviation of 0.2 kg/week (Assali et al., 1999). Using these assumptions, a sample of 72 patients would have adequate power to exclude a reduction in weight gain from 0.3 kg/week to 0.2 kg/week.

We calculated the proportion of participants taking the trial medication, receiving behavioural support, and those who had quit smoking at each time point in each trial arm. We calculated 95% confidence intervals (CI) for the difference in proportions and odds ratios (OR) and 95% CI for the smoking outcomes. Binary logistic regression was used to examine whether the OR for SJW was modified by adjustment for CR use and a multiplicative interaction term was added to examine for effect modification. We calculated the mean weight change from the first visit 2 weeks prior to quit day to visit 7 (4 weeks post quit) for participants achieving Russell standard abstinence at 4 weeks and 6 months, calculating 95% confidence intervals for the difference using the t-distribution. We examined whether SJW confounded the effect of CR on weight gain by stratified analysis, combining differences using weighted mean difference and examined the stratified results for effect modification. Medication side effects were counted as present if a participant recorded the symptom at least once throughout the whole clinic period (2 weeks prior to quit day to 4 weeks afterward) and examined the statistical significance of the differences using a Fisher's exact test. Guidelines advise measuring withdrawal in abstinent smokers only (Shiffman et al., 2004), which we defined as CO reading less than 10 ppm at the relevant visit, which avoided excluding many participants. Differences in individual MPSS scores were tested using a Mann–Whitney *U*-test. Linear regression was used