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Letter to the editor

Response to Covey

Brian Hitsman, Bonnie Spring, Belinda Borrelli, Dennis McChargue, Raymond Niaura

To the Editor:

Dr. Covey asserts that our meta-analysis of the association between history of major depression and smoking treatment outcome (Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003) was flawed because we did not limit our analysis to participants randomized to placebo or alternative least intensive treatment condition. Hitsman et al. (2003) reported a lack of association between history of major depression and treatment outcome, for both short- (≤ 3 months) and long-term (≥ 6 months) abstinence. The effect size estimate for short-term abstinence was statistically nonsignificant and near zero, $d_+ = -.05$, 95% confidence interval (CI) = $-.14, -.04$, $p = .18$. Only two of 13 studies showed a significant association between history of depression and short-term abstinence. Similarly, the effect size for long-term abstinence was statistically nonsignificant and approached zero, $d_+ = -.05$, 95% CI = $-.15, -.04$, $p = .21$, with only one of 12 studies reporting a significant association.

In support of her claim, Dr. Covey cites a bupropion study by Smith et al. (2003), unpublished when we prepared our meta-analysis, which reported that placebo-treated smokers with a history of major depression were significantly less likely than history negative smokers to achieve either short- or long-term abstinence.

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To address Dr. Covey's concern, we re-analyzed the original data restricting the sample in each study to participants randomized to placebo or alternative least intensive treatment condition.¹ Next, we performed a re-analysis further restricted to placebo or the least intensive treatment condition of those studies that specifically tested an antidepressant treatment (antidepressant medications or mood management treatment).² Finally, although our call for manuscripts under review or in press did not elicit the Smith et al. (2003) study, we report both sets of meta-analyses with and without the Smith et al. (2003) study.

¹The placebo or least intensive treatment condition for the studies in Hitsman et al. (2003) are as follows: placebo clonidine + intensive behavioral treatment (Glassman et al., 1988; Covey et al., 1993; Glassman et al., 1993), psychoeducation + nicotine gum (Hall, Muñoz, & Reus, 1994), relapse prevention + aversive smoking (Ginsberg et al., 1995), health education + nicotine gum (Hall et al., 1996), psychoeducation mail intervention (Muñoz et al., 1997), placebo nortriptyline + health education (Hall et al., 1998), placebo naltrexone + intensive behavioral treatment (Covey, Glassman, & Stetner, 1999), placebo bupropion + brief behavioral treatment (Hayford et al., 1999), minimal behavioral treatment (Niaura et al., 1999), placebo paroxetine + nicotine patch + brief behavioral treatment (Killen et al., 2000), and placebo fluoxetine + intensive behavioral treatment (Keuthen et al., 2000). For the study by Smith et al. (2003), the least intensive treatment condition was placebo bupropion + placebo patch + brief behavioral treatment.

²The sample of studies for the "antidepressant studies only" re-analysis included the studies involving paroxetine (Killen et al., 2000), fluoxetine (Keuthen et al., 2000), bupropion (Hayford et al., 1999), nortriptyline (Hall et al., 1998), and mood management treatment (Hall et al., 1994; Hall et al., 1996; Muñoz et al., 1997). As in the re-analysis of the original studies, this analysis was conducted with and without the bupropion study by Smith et al. (2003).

Table 1. Results of the re-analysis of effect sizes of short-term abstinence for smokers positive vs. negative for history of depression treated with placebo or alternative least intensive condition.

Sample for analysis	No. studies	No. subjects <i>N</i> (Hx+/Hx-)	d_+	95% <i>CI</i>	p^a	Q_w	p^b
All treatment trials	13	1215 (413/802)	-.08	-.20, .04	.16	11.43	.49
+ Smith et al. (2003)	14	1375 (438/937)	-.10	-.22, .02	.07	12.51	.49
Antidepressant trials only	7	521 (147/374)	-.01	-.21, .18	.87	1.66	.95
+ Smith et al. (2003)	8	681 (172/509)	-.07	-.25, .11	.37	3.23	.86

d_+ , aggregated effect size estimates; *CI*, confidence interval for the aggregated effect size estimate; Q_w , within-class homogeneity statistic.

^a p value for significance level of the aggregated effect size.

^b p value for test of within-class homogeneity (nonsignificant value reflects a homogeneous estimate, in which the variability around the aggregated effect size is no greater than that expected from sample error alone).

As in Hitsman et al. (2003), we extracted data on point-prevalence abstinence that had been derived on an intent-to-treat basis for the least intensive treatment arm. Effect size estimates were weighted by study sample sizes. A negative sign indicated lower abstinence rates for history positive smokers. Following Cohen's (1987) classification guideline, a small effect is .20, a medium effect is .50, and a large effect is .80. The placebo-controlled nortriptyline study by Prochazka et al. (1998) could not be included in the re-analysis because no data were reported on history of depression \times treatment condition.

Table 1 shows the association between history of major depression and cessation outcome for the least intensive treatment. Re-analysis of the sample of studies in Hitsman et al. (2003) revealed a small and nonsignificant association between depression history and short-term abstinence among participants receiving placebo or alternative least intensive treatment. Re-analysis including Smith et al. (2003) did not change either the magnitude or statistical significance of the aggregated effect size. Re-analysis of antidepressant treatment studies with and without Smith et al. (2003) also yielded similar results. The tests of homogeneity for these analyses indicated a consistency among individual study effect sizes.

Table 2, which displays the effect size estimates for the parallel long-term outcomes, shows a similar pattern of results. Re-analysis of the sample of studies

in Hitsman et al. (2003) revealed a homogeneous effect size that was small and statistically nonsignificant. These results, which were unchanged by adding the study by Smith et al. (2003) or by restricting the meta-analysis to studies involving depression treatment, again indicate that there is no statistically significant difference in long-term abstinence between smokers positive versus negative for history of depression. The aggregate effect size estimates obtained in the re-analysis of long-term abstinence, although statistically nonsignificant, are in general slightly larger in magnitude than those obtained for short-term abstinence.

The epidemiological study (Murphy, Horton, Monson, Laird, Sobol, & Leighton 2003) that Dr. Covey cites as contradicting Hitsman et al (2003) is irrelevant because the current debate focuses on smoking cessation treatment outcome. Murphy et al.'s (2003) data do not permit causal inferences to be drawn regarding the influence of depression history on smoking cessation, since they do not establish the temporality of depression onset vis-à-vis cessation. As Murphy and colleagues rightly noted, "it was possible that some of the subjects who became depressed had already quit smoking before the onset of depression" (p. 1666).

In sum, this re-analysis of short- and long-term abstinence involving only placebo or alternative least intensive treatment condition yields effect size estimates

Table 2. Results of the re-analysis of effect sizes of long-term abstinence for smokers positive vs. negative for history of depression treated with placebo or alternative least intensive condition.

Sample for analysis	No. studies	No. subjects <i>N</i> (Hx+/Hx-)	d_+	95% <i>CI</i>	p^a	Q_w	p^b
All treatment trials	10	774 (254/520)	-.10	-.26, .06	.16	2.54	.98
+ Smith et al. (2003)	11	934 (279/655)	-.12	-.26, .03	.07	2.94	.98
Antidepressant trials only	7	521 (147/374)	-.14	-.34, .06	.12	0.52	.99
+ Smith et al. (2003)	8	681 (172/509)	-.16	-.34, .02	.07	0.74	.99

d_+ , aggregated effect size estimates; *CI*, confidence interval for the aggregated effect size estimate; Q_w , within-class homogeneity statistic.

^a p value for significance level of the aggregated effect size.

^b p value for test of within-class homogeneity (nonsignificant value reflects a homogeneous estimate, in which the variability around the aggregated effect size is no greater than that expected from sample error alone).

that are entirely consistent with those reported in Hitsman et al. (2003), which collapsed across least and most intensive intervention conditions. Again, the effect sizes are statistically nonsignificant and below Cohen's (1987) minimum standard for a small effect size ($d_+ = .20$). It is important to point out that, even if statistical significance had been reached, it is unlikely that effect sizes of the magnitude observed ($d_+ \leq -.16$) would be meaningful clinically. Thus, although we agree with Dr. Covey that restricting the meta-analysis to participants randomized to the least intensive treatment conditions provides a more valid estimate of depression history's association with treatment outcome, doing so does not change our findings. The evidence again suggests that "lifetime history of major depression does not appear to be an independent risk factor for cessation failure in smoking cessation treatment" (from abstract).

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