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Q/ Does any antidepressant besides bupropion help smokers quit?

EVIDENCE-BASED ANSWER

A/ **YES,** nortriptyline approximately doubles smoking cessation rates, an effect comparable to bupropion. Adding nortriptyline to nicotine replacement therapy (NRT) doesn't improve rates further (strength of recommendation [SOR]: **A**, systematic review of randomized controlled trials [RCTs]).

Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram), venlafaxine, monoamine oxidase inhibitors (MAOIs; moclobemide, selegiline), doxepin, and St. John's wort don't improve smoking cessation rates (SOR: **A**, systematic reviews and RCTs).

Evidence summary

Bupropion is the only Food and Drug Administration (FDA)-approved antidepressant recommended as a first-line pharmacologic agent to assist with smoking cessation, based in part on a meta-analysis of 44 placebo-controlled RCTs (13,728 patients), which found that bupropion had a relative risk (RR) of 1.62 for smoking cessation compared with placebo (95% confidence interval [CI], 1.49-1.76). Bupropion produced quit rates that were approximately double those of placebo rates (18% [range 4%-43%] for bupropion vs 9% [range 0%-18%] for placebo).[1]

Nortriptyline is also effective, other antidepressants not so much

A Cochrane systematic review of 10 antidepressants used for smoking cessation included 64 placebo-controlled trials, measuring at least 6-month abstinence rates as primary outcomes, and monitoring biochemical markers (such as breath carbon monoxide and urinary cotinine) to verify abstinence. Some trials included participants with previous depressive episodes, but most didn't enroll patients with active major depression.[1] The **TABLE**[1] gives an overview of the studies and outcomes.

Nortriptyline, which was evaluated in 6 trials, was the only antidepressant besides bupropion that was superior to placebo.[1] Two of the nortriptyline trials included participants with active depression and the other trials had participants with a history of depression. One trial found no difference in quit rates for patients taking nortriptyline with or without a history of major depression, although the subgroups were small. Two trials measured quit rates for 12 months whereas the other 4 trials used 6-month quit rates.

Four additional RCTs with 1644 patients that combined nortriptyline with NRT found no improvement in quit rates compared with NRT alone (RR=1.21; 95% CI, 0.94-1.55).[1] Three RCTs with 417 patients compared bupropion with nortriptyline and found no difference (RR=1.3; 95% CI, 0.93-1.8).[1]

SSRIs. None of the 4 SSRIs investigated in the trials (fluoxetine, paroxetine, sertraline, citalopram) improved smoking cessa-

TABLE

Antidepressants for smoking cessation: Quit rates compared with placebo[1]

Antidepressant	Dose	RCTs, N	Patients, N	RR (for smoking cessation)	95% CI
Bupropion	150 mg twice daily	44	13,728	1.62	1.49-1.76
Nortriptyline	75-100 mg/d	6	975	2.03	1.48-2.78
Fluoxetine	20-60 mg/d	2	1236	0.92*	0.65-1.30
Paroxetine	20-40 mg/d	1	224	1.08*	0.64-1.82
Sertraline	200 mg/d	1	134	0.71*	0.30-1.64
Citalopram	20-40 mg/d	1	17	0.68*	Not available
Venlafaxine	225 mg/d	1	147	1.22*	0.64-2.32
Moclobemide	200-400 mg/d	1	88	1.57*	0.67-3.68
Selegiline	10 mg/d	5	739	1.25*	0.88-1.78
Doxepin	150 mg/d	1	19	No benefit	Not applicable
St. John's wort	300-600 mg/d	2	261	0.81*	0.26-2.53

CI, confidence interval; RCTs, randomized controlled trials; RR, relative risk.
*Not statistically significant.

tion rates more than placebo.[1] The 5 RCTs that studied the drugs followed participants for as long as a year. None of the participants were depressed at the time of the studies, although some had a history of depression.

The sertraline RCT used individual counseling sessions in conjunction with either sertraline or placebo. All participants had a history of major depression.

The paroxetine trial used NRT in all patients randomized to either paroxetine or placebo.

Venlafaxine. The serotonin-norepinephrine reuptake inhibitor venlafaxine didn't improve smoking cessation rates over 12 months.[1]

MAOIs. Neither of the 2 MAOIs increased smoking cessation rates.[1] The moclobemide RCT followed participants for 12 months; the 5 selegiline RCTs followed participants for as long as 6 months.

Other antidepressants. An RCT with 19 participants found that doxepin didn't improve smoking cessation at 2 months.[1] One RCT and one open, randomized trial of St. John's wort found no benefit for smoking cessation.[1,2]

Recommendations

The United States Public Health Service (USPHS) and the University of Michigan Health System (UMHS) guidelines recommend the following FDA-approved pharmacotherapies as first-line agents for smoking cessation: sustained-release bupropion, NRT (gum, inhaler, lozenge, nasal spray, or patch), and varenicline.[3,4] They say that clonidine and nortriptyline are also effective but recommend them as second-line agents because these drugs lack FDA approval for this purpose.

The USPHS also recommends combinations of NRT and bupropion for long-term use. Because of additional cost and limited benefit, UMHS recommends reserving NRT-bupropion combination therapy for highly addicted tobacco users who have several failed quit attempts.

The United States Preventive Services Task Force guideline emphasizes counseling and interventions to prevent tobacco use; it doesn't provide recommendations for pharmacotherapy.[5] It does cite the same agents recommended by USPHS and UMHS as effective. JFP

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Combining nortriptyline and nicotine replacement therapy (NRT) doesn't increase quit rates compared with NRT alone.

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References

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