Review: β-blockers increase fatigue and sexual dysfunction but not depression after myocardial infarction

Ko DT, Hebert PR, Coffey CS, et al. **β-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction.** JAMA. 2002;288:351-7.

QUESTION

In patients who have had myocardial infarction, heart failure, or hypertension, do β-blockers increase depressive symptoms, fatigue, and sexual dysfunction?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 through 2001) and by scanning reference lists.

STUDY SELECTION

English-language studies were selected if they were randomized controlled trials with a placebo comparison, were not crossover trials, enrolled ≥ 100 patients, and had ≥ 6 months of follow-up.

DATA EXTRACTION

Data were extracted on number of patients; presence of heart failure, hypertension, or myocardial infarction; length of follow-up; type of β-blocker; and patient-reported adverse events (i.e., depressive symptoms, fatigue, and sexual dysfunction).

MAIN RESULTS

15 studies (42 409 patients) were included. Follow-up ranged from 6 to 59 months. β-blockers led to an increase in fatigue (10 studies, 17 682 patients); no difference existed between β-blockers and placebo for depressive symptoms (7 studies, 10 662 patients) or sexual dysfunction (6 studies, 14 897 patients) (Table). Withdrawals because of fatigue (10 studies, 29 454 patients) and sexual dysfunction (4 studies, 11 260 patients) were higher in the β-blocker group than in the placebo group; withdrawals for depressive symptoms did not differ between groups (4 studies, 5803 patients) (Table).

CONCLUSIONS

In patients who have had myocardial infarction, hypertension, or heart failure, β-blockers increase fatigue and withdrawals because of fatigue or sexual dysfunction. β-blockers do not increase depressive symptoms.

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β-blockers vs placebo in myocardial infarction at ≥ 6 months*

Outcomes	Number of trials	Weighted event rates		RRI (95% CI)	NNH (CI)
		β-blockers	Placebo		
Fatigue	10	34%	30%	15% (5 to 26)	31 (20 to 74)
Withdrawal because of fatigue	10	1.8%	0.5%	163% (16 to 494)	75 (43 to 308)
Sexual dysfunction	6	19%	17%	10% (–4 to 25)	Not significant
Withdrawal because of sexual dysfunction	4	1.2%	0.3%	397% (203 to 716)	438 per year†
Depressive symptoms	7	21.7%	20.5%	12% (–11 to 41)	Not significant
				RRR (CI)	NNT
Withdrawal because of depressive symptoms	4	0.5%	0.5%	6% (–101 to 56)	Not significant

*Abbreviations defined in Glossary; weighted event rates, NNT, NNH, and CI calculated from data in article using a random-effects model.
†Data provided by author in article.

COMMENTARY

β-noradrenergic antagonists have broad utility, but they are considered to have troublesome side effects. Ko and colleagues found that β-blockers were associated with increased fatigue and increased withdrawal because of fatigue or sexual dysfunction. Yet, closer examination sheds doubt on whether the evidence supports differential effects across the 3 problems and raises questions about the interpretation of side effects in placebo-controlled trials.

Both placebo and active drug effects ranged widely across studies and were strongly correlated (Table, right). The range across studies dwarfed the relatively small apparent differences between placebo and active drug. The significant difference between placebo and active drug for withdrawal because of fatigue or sexual dysfunction may reflect a true adverse effect of β-blockers, although with sexual dysfunction the difference may not be meaningful because almost all withdrawals were in the same study.

The heterogeneity across trials, with close tracking of placebo and active-drug effects, is consistent with a nocebo effect, whereby negative expectations can result in unfavorable outcomes (1). Side effects of placebo have been documented to resemble those of the reference drug (2). Patients in randomized clinical trials receive detailed information about potential side effects of the reference drug. This contributes to similar "side effect" rates for active drug and placebo but would not account for the wide range of event rates. Such a range could result from varying sources, including patient characteristics, actual β-blockers used, or study design.

In summary, a prominent apparent nocebo effect probably biases toward underdetection of side effects in placebo-controlled trials. Furthermore, the studies were so heterogeneous in event rates that it is difficult to interpret their results in combination. Even with these biasing factors, differences in the incidence of fatigue and sexual dysfunction emerge.

Adverse effects of β-blockers

Type of adverse effects		Active drug	Placebo	Correlation*
Depression	Complaint	2.2% to 40%	0% to 39.8%	0.977
	Withdrawal	0% to 1.9%	0% to 2.6%	0.998
Fatigue	Complaint	1% to 66.8%	0.7% to 62.1%	0.987
	Withdrawal	0.4% to 5.1%	0.1% to 2.6%	0.505
Sexual dysfunction	Complaint	3.8% to 43.2%	4% to 42%	0.982
	Withdrawal	0.2% to 2.2%	0% to 0.4%	Not meaningful

*Correlation calculated from data in article.

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References
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2. **Weihrauch TR, Gauler TC.** Arzneimittelforschung. 1999;49:385-93.

Note: **Please see letter on page 32.**