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

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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?

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Abstract and commentary also published in ACP Journal Club

Data sources

Studies were identified by searching Medline (1966–2001) with the keywords myocardial infarction, heart failure, or hypertension in combination with the keywords adrenergic β antagonists and trial; and by scanning reference lists.

Study selection

English language studies were selected if they were randomised 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 (ie, depressive symptoms, fatigue, and sexual dysfunction).

Main results

15 studies (42 409 patients) were included. Follow up ranged from 6–59 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 1). 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 1).

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.

*Table 1. β blockers v 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.

Table 2. Adverse effects of β blockers

Type of adverse effect		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.

COMMENTARY

β noradrenergic antagonists have broad utility, but they are considered to have troublesome side effects. Ko *et al* 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 2). 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 randomised 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.

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1 Barsky AJ, Saintfort R, Rogers MP, *et al.* Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;**287**:622–7.
2 Weihrauch TR, Gauler TC. Placebo—efficacy and adverse effects in controlled clinical trials. *Arzneimittelforschung* 1999;**49**:385–93.

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

We disagree with Dr Swann that a nocebo effect and a variation in event rates in the studies invalidate the results of our study.[1] Firstly, we disagree that a prominent apparent nocebo effect biases toward underdetection of side effects in placebo controlled trials. The nocebo phenomenon refers to symptoms, physiological changes, or both that follow administration of a placebo that the patients believe to be an active drug.[2] Since patients enrolled in placebo controlled trials are unaware of the medication they receive, the nocebo effect should be equally exerted in both treatment groups. In fact, the nocebo effect furnishes a justification for including placebos in clinical trials because it permits a more accurate appraisal of the side effect profile of the active medication. Without such a placebo comparison, the active medication may be associated with side effects that are the nonspecific consequences of taking any medication.[2] Secondly, we disagree that the variation of event rates observed in the trials may invalidate our results. Since the assessment of side effects is applied equally in both the β blocker and the placebo groups, the estimate of risks of β blockers should not be affected.

The main intent of our study was to provide estimates of risks for side effects that are commonly believed to be substantially related to β blocker therapy, such as depression, fatigue, and sexual dysfunction. Contrary to conventional beliefs, β blockers are not associated with substantial risks for these side effects.

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1 Review: β blockers increase fatigue and sexual dysfunction but not depression after myocardial infarction [Abstract]. *Evidence-Based Medicine* 2003 Jan-Feb;**8**:15. Abstract of: Ko DT, Hebert PR, Coffey CS, *et al*. β-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;**288**:351-7.
2. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002;**287**:622-7.

In response: My commentary on the interesting and useful review by Ko *et al* raised questions about the interpretation of the data. Contrary to their letter, it did not state that their conclusions were invalid (in fact it supported some of them). Their arguments in response to the commentary, however, do not effectively address the concerns raised. Their discussion of the nocebo effect ultimately supports the point of my commentary, stating that "since patients enrolled in placebo-controlled trials are unaware of the medication they received, nocebo effects should be equally exerted in both treatment groups." But it can be difficult to distinguish a nocebo or a placebo effect from a true pharmacological effect; the physiological mechanisms can even be the same.[1] This holds

for both positive and negative expectations.[2,3] Patients enrolled in randomised clinical trials read a detailed informed consent document that describes the potential side effects of the active drug. Side effects of placebo are well documented to resemble those of active drugs.[2,4] Placebo and nocebo effects are therefore not limited to "nonspecific" drug effects. That does not negate the importance or utility of placebo controlled trials, but underscores the fact that nocebo effects may reduce the apparent difference in the rate of side effects in persons randomised to placebo compared with those randomised to the active drug, a general point that must be kept in mind when interpreting placebo controlled trials.[4]

These considerations would tend to bias results conservatively, so the fact that in some instances a difference emerged despite them is cause to believe that a true drug effect exists, although its extent is hard to gauge. The point remains that the rates of the same side effects varied by as much as 60-fold across trials and were correlated between placebo and active drug with an *r* that was generally close to unity, yet the difference between corresponding placebo and active drug side effect rates was generally only a few percent at most. Interpretation of the evidence is therefore compromised by the robust correlation between side effect rates for placebo and active drug (nocebo effect) and by the wide variation in rates across studies, which dwarfed the differences within studies and suggests that the studies were so heterogeneous (whether in design, patient population, drugs used, or some combination) that their interpretability as an aggregate may be problematic.

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1 de la Fuente-Fernandez R, Ruth TJ, Sossi V, et al. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* 2001;293:1164-6.
2 Flaten MA, Simonsen T, Olsen H. Drug-related information generates placebo and nocebo responses that modify the drug response. *Psychosom Med* 1999;61:250-5.
3 Green MW, Taylor MA, Elliman NA, *et al*. Placebo expectancy effects in the relationship between glucose and cognition. *Br J Nutr* 2001;86:173-9.
4 Weihrauch TR, Gauler TC. Placebo—efficacy and adverse effects in controlled clinical trials. *Arzneimittelforschung* 1999;49:385-93.