Review: Good adherence (compared with poor adherence) to drug therapy is associated with a reduction in mortality

Simpson SH, Eurich DT, Majumdar SR, et al. **A meta-analysis of the association between adherence to drug therapy and mortality.** BMJ. 2006;333:15.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆

QUESTION

What is the relation between adherence to drug therapy and mortality, and is there a "healthy adherer effect"?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, AMED, CINAHL, ERIC, HealthSTAR, PsycINFO, and the Web of Science (all from inception to 20 June 2005); and references from textbooks and review articles.

Study selection and assessment: Randomized controlled trials (RCTs) or observational studies in any language that evaluated the association between adherence to drug therapy and mortality, explained the method used to measure adherence, provided a clear definition for good adherence, and stratified patients into good and poor adherence groups. Studies that did not provide the number of deaths in each adherence group were excluded. 8 RCTs (n = 37 701) and 13 cohort studies (n = 9146) met the selection criteria. Analyses were done between good and poor adherence within treatment or placebo groups of RCTs and cohorts.

Outcomes: Mortality.

MAIN RESULTS

Meta-analysis showed that fewer patients with good adherence died than did those with poor adherence; similar results were found when considering adherence to placebo (Table). Good adherence led to a reduction in mortality for beneficial drug therapy and increased mortality for harmful drug therapy (Table).

CONCLUSIONS

Good adherence (compared with poor adherence) to drug therapy is associated with a reduction in mortality. The results for patients treated with placebo support the hypothesis of the "healthy adherer effect."

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Association between adherence to drug therapy or placebo and mortality*

Variable	Number of studies (n)	Odds ratio (95% CI)
Good adherence vs poor adherence	21 (46 847)	0.56 (0.50 to 0.63)
Good adherence vs poor adherence to placebo	8 (19 633)	0.56 (0.43 to 0.74)
Good adherence vs poor adherence to beneficial drug therapy	19 (26 436)	0.55 (0.49 to 0.62)
Good adherence vs poor adherence to harmful drug therapy	2 (778)	2.90 (1.04 to 8.11)

*CI defined in Glossary. A random-effects model was used.

COMMENTARY

The very sobering review by Simpson and colleagues follows up on the observation that patients who comply well with placebo have better outcomes than those who do not. The meta-analysis of 21 studies (RCTs and observational studies) of several diseases and drug classes reported a dramatic association between compliance and the clearest endpoint in all of medicine—death. The most striking findings came from the placebo groups of 8 RCTs, comprising 19 633 patients. Good adherence to a totally inert therapy was associated with a near-halving of the risk for death (odds ratio 0.56). Few active substances in our pharmacopoeia produce this magnitude of life-saving benefit.

Observational (cohort) studies that followed patients' use of medications over time found similarly reduced mortality rates in good compared with poor compliers, often beyond any reported life-saving effects of the drugs. Conversely, in 2 RCTs that ultimately showed harm, good adherence in the active drug group was associated with a near-tripling of mortality.

The review is the largest documentation to date of the "healthy adherer effect," an issue that is vastly underappreciated in interpreting drug studies, especially observational ones. Patients who comply well with one medication are likely to do so with their other drugs, and also with nondrug regimens, such as diet and exercise, and use of preventive tests. They are also likely to be less frail, more health-conscious, and more cognitively intact—all factors that independently reduce adverse outcomes. This may help explain why "current users" of estrogen (good compliers) had fewer myocardial infarctions in observational studies than nonusers or former users (1). The same effect should also make us skeptical of the degree of association between lower fracture rates in good compliers with osteoporosis medications compared with poor compliers. However, the "healthy adherer effect" has limits, since this study also showed that it could be overcome by adherence to clearly harmful drugs.

Further work is needed to help us understand exactly what clinical characteristics account for the "healthy adherence effect" and how many may be modifiable. If any of the factors could be influenced by clinicians, it could have an effect on mortality that would dwarf that of many of the drugs we commonly prescribe.

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Reference

1. **Grodstein F, Manson JE, Colditz GA, et al.** A prospective observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med. 2000;133:933-41.