Music, imagery, touch, and prayer as adjuncts to interventional cardiac care: the Monitoring and Actualisation of Noetic Trainings (MANTRA) II randomised study

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Summary

Background **Data from a pilot study suggested that noetic therapies—healing practices that are not mediated by tangible elements—can reduce preprocedural distress and might affect outcomes in patients undergoing percutaneous coronary intervention. We undertook a multicentre, prospective trial of two such practices: intercessory prayer and music, imagery, and touch (MIT) therapy.**

Methods **748 patients undergoing percutaneous coronary intervention or elective catheterisation in nine USA centres were assigned in a 2×2 factorial randomisation either off-site prayer by established congregations of various religions or no off-site prayer (double-blinded) and MIT therapy or none (unmasked). The primary endpoint was combined in-hospital major adverse cardiovascular events and 6-month readmission or death. Prespecified secondary endpoints were 6-month major adverse cardiovascular events, 6-month death or readmission, and 6-month mortality.**

Findings **371 patients were assigned prayer and 377 no prayer; 374 were assigned MIT therapy and 374 no MIT therapy. The factorial distribution was: standard care only, 192; prayer only, 182; MIT therapy only, 185; and both prayer and MIT therapy, 189. No significant difference was found for the primary composite endpoint in any treatment comparison. Mortality at 6 months was lower with MIT therapy than with no MIT therapy (hazard ratio 0·35 (95% CI 0·15–0·82, p=0·016).**

Interpretation **Neither masked prayer nor MIT therapy significantly improved clinical outcome after elective catheterisation or percutaneous coronary intervention.**

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Introduction

In 2001, the US National Center for Complementary and Alternative Medicine defined "frontier medicine" as those therapies "for which there is no plausible biomedical explanation".[1] Examples cited included bioelectromagnetic therapy, biofield and energy healing, homoeopathy, and therapeutic prayer or spiritual healing. Although these therapies are used extensively by the general population, few high-quality data are available to elucidate the mechanisms underlying these approaches or to prove their safety or effectiveness. Epidemiological findings clearly suggest that mood, hostility, depression, and spiritual affiliation are all associated with cardiovascular outcomes,[2–5] but the effect of frontier therapies on disease natural histories remains undefined.

We examined the effect of these therapies on patients with coronary-artery disease. Patients undergoing cardiac catheterisation with a view to percutaneous coronary intervention are informed about risks, including death, and are awake during the procedure. With predictable periods of distress, noetic therapies might be useful to induce vasodilation, to slow the heart rate, to calm the mind,[6] or to promote healing through undefined mechanisms. Noetic interventions, defined as therapies for which the method of administration does not use a tangible drug or medical device were explored in the MANTRA I pilot study,[7] in which there was a measurable reduction in preprocedure distress[8] that might affect clinical outcomes.[9] Limitations of the pilot study included limited power, enrolment of exclusively male patients at a single centre, and the inability to assess combinations of several noetic modalities. The MANTRA II study was designed to address these limitations.

Methods

Design

Nine US centres participated (webappendix 1). In all centres, approval by the institutional review board was obtained. Informed consent, listing participating prayer groups, was obtained from all patients.[7] The study design was a 2×2 factorial randomisation scheme (figure 1). Patients were randomly assigned bedside noetic intervention (music, imagery, and touch [MIT] therapy) or no intervention, and sites were informed of the assignment. Patients were simultaneously randomly assigned off-site prayer or no off-site prayer, but sites and patients were not informed (double-blind). Telephone randomisation-centre services were provided by Interactive Clinical Technologies Inc (Durham, NC, USA) and the Duke Clinical Research Institute.

See Lancet Online for webappendix 1

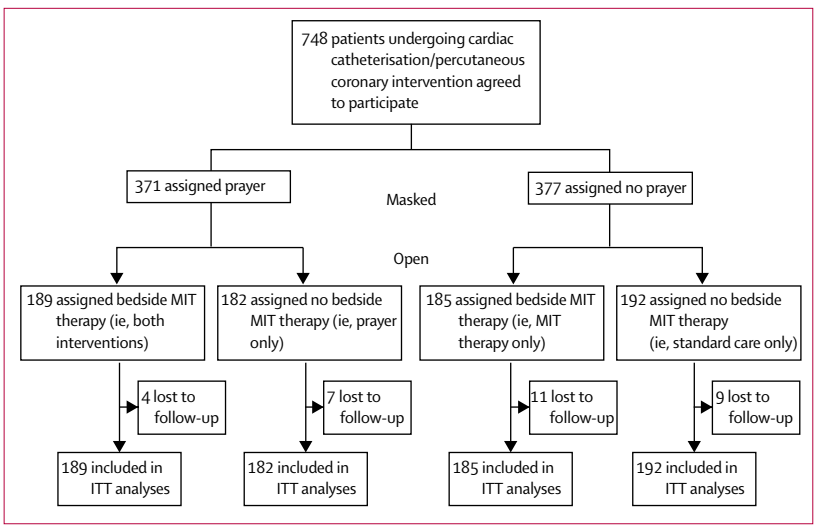

Figure 1: **Trial profile**
2×2 factorial randomisation scheme. ITT=intention to treat.

See Lancet Online for webappendices 2 and 3 and webtable

After a 3-month period of non-enrolment after the events of Sept 11, 2001, a conference of the MANTRA II steering committee, national advisory board (webappendix 2), and data safety and monitoring board (webappendix 3) was convened to discuss the effect of these events on the study's final year. The meeting also considered both the interim recommendation of the data safety and monitoring board to continue enrolment and an independent report of an effective prayer structure in another prospective, masked, randomised trial.[10] The consensus decision was, rather than to terminate the trial prematurely, to amend the protocol in an attempt to stimulate study enrolment by changing to a "high-dose" or two-tiered prayer strategy.

All patients undergoing elective percutaneous coronary intervention or elective catheterisation with possible percutaneous coronary intervention were candidates. The protocol did not stipulate any maximum or minimum age.

Procedures

Procedures were done according to each institution's standard practice. All decisions to proceed from catheterisation to percutaneous coronary intervention were based on clinical judgment.

For patients assigned MIT therapy a 40 min open bedside session was undertaken after enrolment and before percutaneous coronary intervention by a practitioner certified in Level 1 Healing Touch.[11] After rapport between practitioner and patient had been established, the patient was taught relaxed abdominal breathing, chose a preferred place image (defined as the most beautiful, peaceful place he or she had ever been), and selected a musical preference (easy listening, classical, or country music). Identical cassette-tape music-imagery scripts were used for all patients in all sites. After the imagery script, the practitioner applied 21 Healing Touch hand positions, each for 45 s.[12] The patient could then wear the headphones with musical background during the percutaneous coronary intervention.

During the first 2 years of the study, the name, age, and illness of each patient assigned prayer therapy were provided to each of the 12 primary-tier prayer groups. All prayer groups were notified directly through the prayer-therapy coordinator at the randomisation centre within 30 min of randomisation. Timing and content of prayers were defined by the routine practices of each prayer group, with durations ranging from 5 days to 30 days after enrolment. Prayer groups were all established congregations. Documentation of prayer-group adherence to the protocol was not mandated. Primary-tier prayer groups included Christian, Muslim, Jewish, and Buddhist groups (webtable).

In the final year of enrolment, for the two-tiered prayer therapy, an additional 12 prayer groups were added in emulation of methods previously published.[10] The second-tier groups were given details of the MANTRA II study design and a list of the primary-tier prayer congregations. When a patient was assigned prayer therapy, the second-tier groups were not given information on the name, age, or illness but were simply notified that a patient had been enrolled and asked to pray for the prayers of the primary-tier congregations.

Endpoints

Protocol follow-up was specified at 6 months after randomisation. The primary study endpoint was in-hospital major adverse cardiovascular events or death or any readmission to hospital within the next 6 months. Prespecified secondary endpoints were major adverse cardiovascular events, death or readmission, and mortality, each within the following 6 months. Major adverse cardiovascular events included death, new myocardial infarction as defined by electrocardiography or a rise in creatine phosphokinase to more than twice the upper limit of normal, new congestive heart failure, repeat percutaneous coronary intervention, or coronary bypass surgery.

On study enrolment, the Spielberger state-trait anxiety survey[13] and the Duke religiosity survey[14] were completed by all patients to create self-characterised scores of anxiety and religiosity. Self-rated assessments of mood by a previously described visual analogue scale[8] were completed on enrolment and before percutaneous coronary intervention to characterise "distress".[8,9] A unique, non-standardised questionnaire was administered before discharge to assess whether the patient believed he or she had been assigned off-site prayer therapy.

Statistical analysis

The sample size for MANTRA II was designed to provide 80% power to detect a 25–30% difference in the primary

	Total (n=748)	Prayer (n=371)	No prayer (n=377)	MIT therapy (n=374)	No MIT therapy (n=374)
Demography					
Median (IQR) age, years	65 (55–73)	65 (56–72)	65 (55–73)	66 (57–74)	63 (55–72)
M/F (%)	534 (71%)/214 (29%)	262 (71%)/109 (29%)	272 (72%)/105 (28%)	266 (71%)/108 (29%)	268 (72%)/106 (28%)
Clinical features					
Diabetes	263 (35%)	130 (35%)	133 (35%)	132 (35%)	131 (35%)
Current smoker	122 (17%)	66 (18%)	56 (15%)	57 (16%)	65 (18%)
Previous MI	302 (41%)	160 (43%)	142 (38%)	146 (39%)	156 (42%)
CHF	113 (15%)	62 (17%)	51 (14%)	53 (14%)	60 (16%)
Psychological features					
Median (IQR) baseline VAS distress	268 (153–400)	268 (161–393)	268 (146–407)	264 (159–401)	274 (151–400)
Median (IQR) Spielberger anxiety score	38 (30–47)	38 (31–47)	38 (30–47)	38 (30–47)	38 (30–47)
Median (IQR) baseline QOL score	56 (48–63)	56 (48–63)	56 (48–63)	57 (48–64)	55 (48–62)
Duke religiosity survey*					
1	316 (43%)	155 (43%)	161 (44%)	170 (47%)	146 (39%)
2	341 (46%)	171 (47%)	170 (46%)	182 (50%)	159 (43%)
3	261 (36%)	129 (36%)	132 (36%)	138 (38%)	123 (33%)
Underwent percutaneous coronary intervention	563 (76%)	274 (74%)	289 (79%)	284 (77%)	279 (76%)
Treatment					
Aspirin	689 (92%)	344 (93%)	345 (92%)	339 (91%)	350 (94%)
Glycoprotein IIb/IIIa inhibitor	89 (12%)	48 (13%)	41 (11%)	49 (13%)	40 (11%)
β blocker	497 (67%)	248 (67%)	249 (66%)	232 (63%)	265 (71%)
ACE inhibitor	322 (43%)	164 (44%)	158 (42%)	148 (40%)	174 (47%)

MI=myocardial infarction; CHF=congestive heart failure; VAS=visual analogue scale; QOL=quality of life; ACE=angiotensin-converting enzyme. Data are number of patients unless otherwise stated. *1=attends church at least once a week (social); 2=prays at least once a day (personal practice); 3=definitely experiences presence of the Divine, definitely feels that religious/spiritual beliefs are behind his or her whole approach to life, and religion definitely carries over into all other dealings in his or her life.

Table 1: **Baseline features and randomised groups**

composite endpoint, on the assumption of a 6-month event rate in the control group of 35%.[7] Permuted block randomisation stratified by clinical site was used.

All treatment comparisons were by intention to treat, and statistical tests were two-sided with $\alpha=0\cdot05$. Cumulative event rates were calculated by the Kaplan-Meier method. Time to event was derived from time of randomisation. Significance of treatment-group differences was assessed by a Cox's proportional-hazards model truncated at 180 days. Comparison of prayer and no-prayer groups was adjusted for MIT therapy, and comparison of MIT-therapy and no-MIT-therapy groups was adjusted for prayer and for clinical outcomes. Relative risks, expressed as hazard ratios with associated 95% CI, were derived from the Cox's model. This model was also used to test for interaction between prayer and MIT therapy. Treatment groups were compared for reduction in distress before percutaneous coronary intervention by use of Wilcoxon's rank-sum test. Statistical analyses used SAS (version 8.2).

Sensitivity analyses were done for all patients with missing outcome follow-up. Primary endpoint outcomes were set to an event for patients in the treatment group and to no event for patients in the control group; these imputations were subsequently reversed. This procedure was used for both treatment-group comparisons.

Role of funding source

No funding source had any direct role in the study design; in the collection, analysis, or interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

748 patients were enrolled between May, 1999, and December, 2002. 737 (99%) underwent cardiac

Endpoint	Number with event (Kaplan-Meier event rate; 95% CI)		Hazard ratio (95% CI)	p*	Number with event (Kaplan-Meier event rate; 95% CI)		Hazard ratio (95% CI)	p*
	MIT therapy (n=374)	No MIT therapy (n=374)			Prayer (n=371)	No prayer (n=377)		
Primary composite	135 (38%; 33–43)	128 (36%; (31–41)	1·09 (0·86–1·39)	0·4714	130 (37%; 32–42)	133 (37%; 32–42)	0·97 (0·77–1·24)	0·8351
6-month MACE	86 (24%; 19–28)	93 (26%; 21–30)	0·94 (0·70–1·25)	0·6568	82 (23%; 18–27)	97 (27%; 22–31)	0·85 (0·63–1·14)	0·2785
6-month death and readmission	117 (33%; 28–38)	121 (34%; 29–39)	0·97 (0·75–1·25)	0·8253	115 (33%; 28–37)	123 (35%; 30–40)	0·93 (0·72–1·19)	0·5220
6-month death	7 (2%; 0·5–3)	20 (6%; 3–8)	0·35 (0·15–0·82)	0·0156	14 (4%; 2–6)	13 (3%; 1–5)	1·13 (0·53–2·4)	0·7531

MACE=major adverse cardiovascular events. *From adjusted Cox's proportional-hazards model.

Table 2: **Primary and secondary endpoints for groups assigned MIT therapy versus no MIT therapy and prayer versus no prayer***

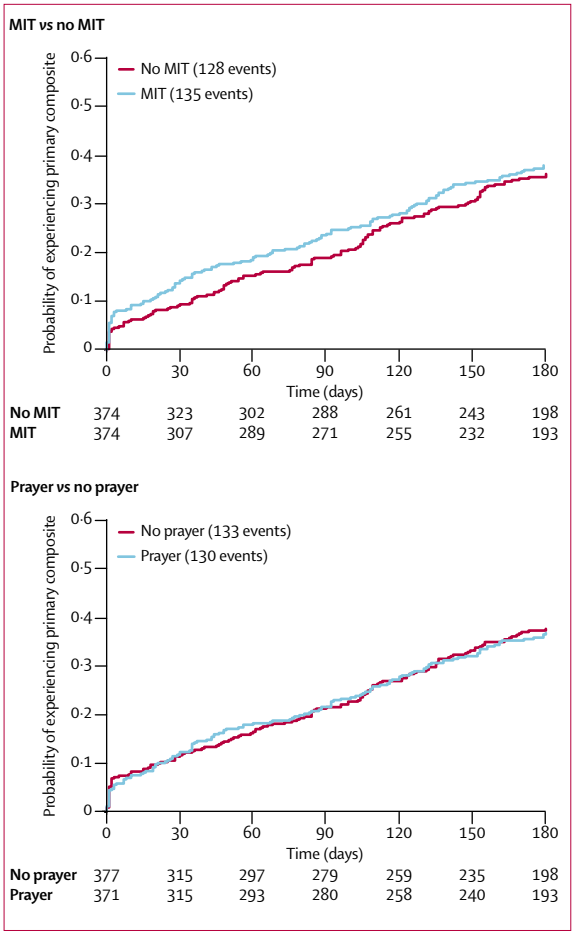

Figure 2: **Kaplan-Meier probability of experiencing primary composite endpoint for MIT therapy versus no MIT therapy and for prayer versus no prayer**

catheterisation and 563 (75%) percutaneous coronary intervention. Inhibitors of glycoprotein IIb/IIIa were used in 341 (61%) of the 563 patients undergoing percutaneous coronary intervention. Baseline demographic characteristics and clinical features, interventional procedures, and baseline measures of mood, anxiety, spirituality, and quality of life were well balanced across the treatments (table 1).

Questionnaires completed by the patients at enrolment showed that 613 (89%) of 688 responding were aware of prayer on their behalf outside of the protocol. Questionnaires completed before discharge showed that 186 (64%) of 292 who were not assigned prayer treatment believed that they were, whereas 98 (35%) of 278 who were assigned prayer according to the protocol believed that they were not.

Complete 6-month follow-up data were obtained for 717 (96%) of the 748 patients enrolled. Six patients withdrew consent, and 25 were not available for follow-up. Information on the primary endpoint was missing in 15 (4%) of patients assigned MIT therapy and 16 (4%) assigned no MIT therapy, and in 11 (3%) assigned prayer versus 20 (5%) assigned no prayer. Sensitivity analyses imputing outcomes for patients with missing endpoint data did not change the interpretation of study results for any treatment-group comparisons. Of the patients with complete follow-up, the primary composite endpoint occurred overall in 263 (37%) patients; 179 (24%) had major adverse cardiovascular events, 238 (33%) were readmitted to hospital or died, and 27 (4%) died within 6 months.

Frequencies and hazard ratios for primary and prespecified secondary endpoints for the groups assigned MIT therapy and no MIT therapy are shown in table 2, and Kaplan-Meier curves of cumulative frequency for the primary composite endpoint are shown in figure 2. There were no differences between the MIT-therapy and no-MIT-therapy groups in composite primary or secondary endpoints (table 2). Self-rated distress before the percutaneous coronary intervention was significantly lowered in the MIT-therapy group compared with the no-MIT-therapy group (median –84·2 [IQR –155·2 to –14·0] *vs* –18·9 [–60·0 to 19·0]; $p<0·0001$). 6-month mortality was lower in patients assigned MIT therapy than for those assigned no MIT therapy (table 2).

Frequencies and hazard ratios for primary and prespecified secondary endpoints for the groups assigned prayer or no prayer are shown in table 2. There were no differences in any of the primary or secondary endpoints between these groups. There was no difference in the timing of events for the primary outcome (figure 2).

Over the final 7 months of the study the two-tiered prayer therapy was assigned to 84 patients, with 88 assigned no protocol prayer. Hazard ratios for the

Endpoint	Number with event (Kaplan-Meier event rate; 95% CI)		Hazard ratio (95% CI)	p*
	Two-tiered prayer (n=84)	No prayer (n=88)		
Primary composite	25 (31%; 21–41)	30 (35%; 25–45)	0·83 (0·5–1·4)	0·4823
6-month MACE	17 (21%; 12–30)	18 (21%; 12–30)	1·00 (0·5–1·95)	0·9895
6-month death and readmission	20 (25%; 15–34)	30 (35%; 25–46)	0·62 (0·35–1·09)	0·0979
6-month death	2 (2%; 0–6)	3 (4%; 0–8)	0·73 (0·12–4·4)	0·7287

MACE=major adverse cardiovascular events. *From adjusted Cox's proportional-hazards model.

Table 3: **Primary and secondary endpoints for: no prayer versus two-tiered prayer (subset of patients randomised after two-tier prayer was introduced)**

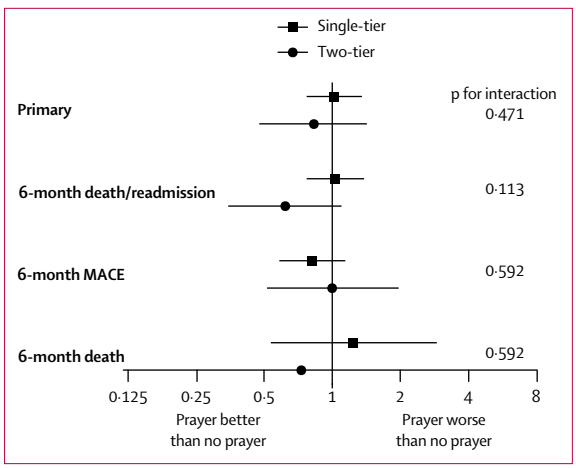

Figure 3: **Hazard ratios for primary and secondary endpoints for single-tier and two-tier prayer versus concomitantly randomised no-prayer controls**

primary and secondary endpoints are shown in table 3 and those for the primary composite and prespecified secondary endpoints for single-tier prayer compared with two-tier prayer, relative to the contemporaneously randomised no-prayer groups, are shown in figure 3. Tests of interaction showed no significant difference in the effects of prayer between the period before the implementation of two-tiered prayer and the period after this change.

Of the 748 patients, 192 were assigned standard care with neither intervention, 182 prayer only, 185 bedside MIT therapy only, and 189 both prayer and MIT therapy. No significant differences were found among these four treatment groups in the primary or secondary composite endpoints (table 4), and there were no significant interactions between MIT therapy and prayer for these endpoints. 6-month mortality was slightly lower in patients assigned both prayer and bedside MIT therapy than in those assigned standard care or prayer only, with hazard ratios of 0·34 (95% CI 0·09–1·25; p=0·10) and 0·26 (95% CI 0·07–0·93; p=0·04).

Discussion

Active bedside compassion and prayers for the sick are widely practised for healing throughout the world. Whether such bedside and remote practices have any effect on clinical outcomes remains controversial.[15] Although these approaches are among the most ancient of healing practices, scientific quantification of the methods, mechanisms, safety, and effectiveness of "frontier medicine" is at a very early stage.

In MANTRA II, we studied two noetic strategies in patients undergoing coronary revascularisation: an unmasked bedside combination of music, imagery, and touch, and a double-masked, off-site array of combined congregational prayers. Neither therapy alone or combined showed any measurable treatment effect on the primary composite endpoint of major adverse cardiovascular events at the index hospital, readmission, and 6-month death or readmission.

The mechanisms through which distant intercessory prayer might convey healing benefit are unknown. Physiological effects seen in individuals who are actively meditating or praying themselves[6,16] might not relate to effects of double-blind administration to others at a distance. Non-local features of consciousness based theoretically around observations in quantum physics[17] might or might not relate to healing. Similarly, although there are many theories about vasodilation, pain relief, and other potentially beneficial effects of music, imagery, and touch in which the patient consciously participates,[6,11,18–20] no definitive mechanistic data are available.

Outcome studies can provide insight or clarify key questions even in the absence of mechanistic knowledge. Prospective, randomised outcome studies of off-site, masked prayer in 2242 patients with heart disease have been published previously.[7,21–23] Of these, 2182 were in cardiac-care units, reported in three studies, each with different primary endpoints.[21–23] Byrd[21] studied good, intermediate, or bad hospital-course ratings in 393 patients in cardiac-care units and reported a 36% reduction in bad ratings with prayer (p<0·01).[21] Harris and colleagues[22] used a non-validated, unique index in 990 patients in cardiac-care units, reporting an 11% reduction in the score with prayer (p=0·04). Aviles and co-workers[23] studied cardiovascular-disease progression after discharge in 799 patients admitted to cardiac-care units, reporting odds ratios for the whole sample and for descriptor-stratified high-risk and low risk cohorts of 0·83 (p=0·25), 0·90 (p=0·90), and 0·65 (p=0·12), respectively.[23] In the fourth study, 150 patients with acute coronary presentations undergoing urgent percutaneous coronary intervention were studied with the use of standard care, double-blind off-site prayer, or one of three unmasked bedside interventions: healing touch, imagery, or stress relaxation.[7] The odds ratio for

Endpoint	Prayer only (n=182)	MIT therapy only (n=185)	Prayer and MIT therapy (n=189)	Standard care (n=192)	p*
Primary composite	63 (36%; 29–43)	68 (39%; 32–46)	67 (37%; 30–44)	65 (36%; 29–43)	0·8312
6-month MACE	43 (24%; 18–30)	47 (26%; 20–32)	39 (21%; 15–27)	50 (27%; 21–33)	0·6771
6-month death and readmission	58 (34%; 26–41)	60 (35%; 28–42)	57 (31%; 25–38)	63 (35%; 28–42)	0·8948
6-month death	11 (6%; 3–10)	4 (2%; 0–4)	3 (2%; 0–3)	9 (5%; 2–8)	0·0716

MACE=major adverse cardiovascular events. *Log-rank test (df=3).

Table 4: **Unadjusted Kaplan-Meier rates for primary and secondary endpoints in factorial treatment groups**

index-admission combined major adverse cardiovascular events or ischaemia on continuous electrocardiographic monitoring among the 30 patients assigned standard care versus the 30 assigned prayer was 0·48 (p=0·32).

Although the primary endpoint in Aviles and colleagues' study is similar to the MANTRA II secondary endpoint of 6-month readmission and death, overall, comparison or pooling of the primary endpoints across these studies is difficult because of their heterogeneity. Furthermore, in an overview of clinical publications on use of "supraphysical energy", "spiritual healing", and "distant healing" Astin and co-workers[24] reviewed 23 studies with a mean methodological Jadad score of 3·6.[25] Heterogeneity of nomenclature, prayer methods, populations of patients, and study designs precluded a meta-analysis. A Cohen's *d* effect weighted for sample size was calculated for the primary endpoint from each study.[26] With 57% of studies showing treatment benefit, Astin and colleagues agreed with a previous review in the Cochrane Database[27] that the current evidence warrants further study, which addresses the methodological issues outlined.[24] In a follow-up to that review, Ernst less systematically supplemented the overview with eight non-randomised and nine randomised studies of distant healing; he concluded that they shifted the weight of evidence against the notion that distant healing is more than a placebo.[28]

One of the most central issues is the absence of knowledge about dosing of noetic therapies. In the three studies discussed above,[21–23] three to seven individuals praying, across a range of Christian traditions, were used. The MANTRA pilot study engaged ten congregations of many religious faiths involving hundreds of individuals.[7] The MANTRA II study again involved many faiths in a larger number of congregations. The issues of whether the number of intercessors praying, whether prayers from individuals differ from those from congregations, or whether prayers from different religions have different effects remain unresolved.

Timing and duration might also influence measurable treatment effects. In published randomised cardiovascular studies, duration of prayer lasted from enrolment to hospital discharge,[21] from enrolment to 30 days after discharge,[7,22] and from discharge for 26 weeks[23] with varying frequencies. Whether notification of prayer groups within 30 min of randomisation produced healing prayers before the percutaneous coronary intervention was completed might have affected the therapeutic benefit in MANTRA II.

In all four published studies of distant prayer, specific information about the patient was provided to the off-site intercessors. In the final year of MANTRA II an additional methodological feature was added; second-tier prayer groups did not receive specific information about the patient but instead were asked to pray for the prayers of other prayer groups. Previous reports and observations have suggested that prayers not seeking specific ends have more profound effect,[6,16] but whether findings related to healing per se[10] can be validated remains unproven.

The investigation of prayer in all studies, including MANTRA II, also presents the challenge of studying only incremental effects, because many would have considered a request to patients or families not to pray for loved ones with heart disease unethical. Off-protocol prayer in the study population could have important effects on the study power. In both the study by Aviles and colleagues and MANTRA II, treatment effects of 25–30% were used for power calculations, and both studies aimed to enrol 750–800 patients. Aviles and co-workers observed a 13% difference in their primary endpoint, but the study was underpowered to demonstrate significance at that level, and the researchers could only speculate on the frequency of off-protocol prayer or placebo effect in their cohort. In our feasibility pilot population, the basis for power calculations for MANTRA II, 39% of patients were aware of off-protocol prayer on their behalf at study entry. In MANTRA II, 89% knew of off-protocol prayer, and two-thirds of patients not assigned protocol prayer believed that they were. Generally, such off-protocol features might be offset by randomisation, but the presence of placebo effect in 67% and off-protocol prayer in almost 90% of the study cohort could have substantially limited the ability to detect incremental treatment effect in MANTRA II.

Many of the same issues apply to our findings with the unmasked, bedside use of MIT therapy. We know of no published randomised outcomes studies in cardiac patients with these interventions, other than the MANTRA feasibility pilot. MANTRA II attempted to standardise the MIT intervention by use of cassette-tape-based music and imagery scripts and practitioner certification across all sites. Nonetheless, there are no known measures for the "dose" delivered.

Although there was significantly less preprocedural distress associated with administration of bedside MIT therapy, we cannot with certainty discern whether the mechanism of this effect relates to the presence of a compassionate human being at the bedside or to any individual component of the treatment strategy (the music, the imagery, or the touch). Furthermore, as others have noted, the most measurable effect of noetic therapies could be in qualitative endpoints rather than clinical outcomes.[23]

The MANTRA study project represents a continuing effort to collect systematic, scientifically structured information on widely practised, intangible therapeutic approaches for which we have essentially no mechanistic understanding. In the absence of knowledge about mechanism or dose, we should emphasise that both ethical and scientific standards for

research on this topic must attend to safety, as well as efficacy considerations, with the use of informed consent and data safety monitoring. Apart from overtly negative prayer or voodoo, even assumptions that well-intended therapies are simply benign could be naive, as has been raised with relief of worry before percutaneous coronary intervention.[9] Although the primary endpoints in this study showed no definitive treatment effects, secondary analyses can be useful for hypothesis generation to guide future trials. MANTRA II was a deliberate shift from single-centre studies using uniquely stylised nomenclature and endpoints to multicentre studies using standard clinical descriptors and outcomes for the prospective, randomised study of noetic interventions. This shift, in concert with recently published guidelines for better studies in spirituality,[29] will support more robust opportunities for pooling of data and meta-analyses across studies, important to the progression of understanding of novel noetic therapies.

Contributors

Mitchell Krucoff, Daniel Mark, Michael Cuffe, James Blankenship, Harold Koenig, Suzanne Crater, Michael Sketch, Kerry Lee, and Mimi Guarneri were responsible for the study's concept and design. Augusto Pichard, Vib Kshettry, Mitchell Krucoff, James Blankenship, Michael Cuffe, Kenneth Morris, Suzanne Crater, Richard Krieger, Michael Sketch, and Mimi Guarneri contributed to acquisition of data. Dianne Gallup, Daniel Mark, Mitchell Krucoff, James Blankenship, Michael Sketch, Kerry Lee, and Mimi Guarneri were responsible for statistical analysis and interpretation. The report was drafted by Mitchell Krucoff, Daniel Mark, Suzanne Crater, and Harold Koenig and revised and finally approved by all the other authors.

Conflict of interest statement

We declare that we have no conflict of interest.

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