

Integrative Medicine

Evidence-based summaries and critical reviews on
the latest developments in integrative therapies [ALERT]

CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Chocolate for Primary Prevention of Atrial Fibrillation

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Dr. Vetrici and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: In a large, population-based, prospective cohort study of Danish people aged 50-64 years, researchers found that chocolate intake was inversely related to incidental rates of atrial fibrillation and atrial flutter.

SOURCE: Mostofsky E, Berg Johansen M, Tjønneland A, et al. Chocolate intake and risk of clinically apparent atrial fibrillation: The Danish diet, cancer, and health study. *Heart* 2017;103:1163-1167.

The most common sustained arrhythmia, atrial fibrillation (AF) is associated with significant morbidity and mortality because of an increased risk of thromboembolism, stroke, heart failure, and cognitive impairment. The U.S. prevalence is 2% in people younger than 65 years of age and 9% in those older than 65 years of age, with people of European descent having higher incidence rates than African Americans.^{1,2} In people of European descent older than 40 years of age,

the lifetime risk of developing AF is 26% in men and 23% in women, and the incidence doubles with every decade of life.^{1,2} The pathophysiology of AF involves a complex inflammatory cascade that generates cytokines and reactive oxygen species, leading to electrical and structural remodeling ultimately resulting in AF.^{3,4}

Cocoa-containing foods show antioxidant, anti-inflammatory, and vasodilatory properties.⁵

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[INSIDE]

Acupuncture for Pain Control
in the Emergency Department

page 136

Acupuncture as Adjunct Therapy
for Infertility in Polycystic Ovary Syndrome

page 140

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Summary Points

- Chocolate consumption on a weekly basis was associated with a significantly reduced risk of atrial fibrillation (AF) in a cohort study of Danish men and women 50-64 years of age who were followed for 13.5 years.
- The highest inverse association was seen at two to six servings per week for men and one serving per week for women.
- The cocoa content of chocolate appears to be important. The authors recommended chocolate that has a high proportion of cocoa solids (at least 30%), correlating with higher levels of cocoa flavonoids.

Ingestion of cocoa flavonoids lowers blood pressure, increases high-density lipoprotein cholesterol, and improves endothelial function.^{5,6} Moderate chocolate consumption is associated with improved markers of cardiovascular health and lower rates of myocardial infarction and heart failure.^{5,6} The neuroprotective and neuromodulatory effects of cocoa flavonoids have been shown to protect human cognition and prevent cognitive decline.⁷

Mostofsky et al set out to determine whether there was an association between chocolate intake and incidental, clinically apparent AF by analyzing data from the Danish Diet, Cancer and Health Study. The authors of this prospective, population-based, cohort study recruited participants from December 1993 to May 1997, and followed them until December 2009. Information about diet and lifestyle was obtained via self-administered questionnaires, including a validated food frequency questionnaire collected at enrollment. Although the questionnaire did not differentiate between milk chocolate and dark chocolate, the authors reported that most of the chocolate consumed in Denmark is milk chocolate, which contains at least 30% cocoa solids as regulated by directive of the European Union.

The cohort subjects were linked to the Danish National Patient Register to identify primary discharge diagnosis for AF or atrial flutter (AFL) from the time of enrollment until December 2009. Participants were excluded for missing chocolate intake, missing inclusion date, multiple confounders, previous

record of AF, and history of cancer at baseline. The final sample comprised 55,502 men and women who enrolled between the ages of 50-64 years and were followed for a median of 13.5 years. Participants were considered at risk from the date of the questionnaire until the first hospital admission for AF, death, emigration, or end of follow-up. During follow-up, there were 3,346 cases of incidental AF, which the authors defined as the total occurrences of AF and AFL combined.

Chocolate intake was modeled consistently with other studies using servings of one-ounce bars or packets of chocolate at < 1 serving/month, 1-3 servings/month, 1 serving/week, 2-6 servings/week, and ≥ 1 serving/day. In each chocolate intake group, the proportion of men was 46.3-48.7% and the mean body mass index (BMI) was 25.1-26.4 kg/m². In each group, fewer than 20% had hypertension (HTN), fewer than 5.4% had type 2 diabetes (DM), fewer than 2% had cardiovascular disease (CVD), and all groups had similar proportions of current smokers (36%), former smokers (29%), and never smokers. About 50% of subjects in each group had total serum cholesterol > 232 mg/dL (> 6 mmol/L).

Multivariate Cox proportional hazard models were constructed to calculate hazard ratios (HR) and confidence intervals (CI). The authors adjusted for potentially confounding variables associated with AF, including sex, BMI, systolic blood pressure, total serum cholesterol, total calories, coffee consumption, alcohol consumption, smoking status, education beyond elementary

school, as well as regularly updated information on HTN, DM, and CVD. Another multivariate model was constructed and adjusted for caffeine intake from other sources, such as tea, coffee, and soft drinks, but the results were almost identical to coffee consumption alone.

The authors noted that subjects with higher levels of chocolate intake also reported higher daily caloric intake, a higher proportion of daily calories from chocolate, and higher levels of educational attainment. The study results showed that the rate of AF was highest in the group consuming the least amount of chocolate. Relative to less than one serving of chocolate per month, the AF rate was lower in those consuming 1-3 servings/month (HR, 0.90; 95% CI, 0.82-0.98), 1 serving/week (HR, 0.83; 95% CI, 0.74-0.92), 2-6 servings/week (HR, 0.80; 95% CI, 0.71-0.91), and ≥ 1 serving/day (HR, 0.84; 95% CI, 0.65-1.09). Men had higher incidence rates at each level compared to women, but a lower risk of AF was observed at higher levels of chocolate consumption in both men and women. For women, the strongest inverse association was noted at 1 serving/week (HR, 0.79; 95% CI, 0.66-0.95); in men, the strongest inverse association occurred at 2-6 servings/week (HR, 0.77; 95% CI, 0.67-0.90).

■ COMMENTARY

This study highlights a potentially new lifestyle modification that may prevent AF and could be easy to follow. Although counterintuitive based on the known cardiovascular stimulant effects of caffeine, data analyses of multiple studies show that modest caffeine intake through coffee and tea is related to AF risk inversely.⁸ Thus, the small amount of caffeine in chocolate might have a similar association.⁸ In the United States, AF treatment costs \$6 billion annually, while patients with AF spend \$8,705 more per year on medical costs than those without AF.¹ Currently, 6 million Americans have AF, and this number is projected to increase to 12 million by 2050.⁹ There are no cures and no proven strategies for primary prevention of AF, but modifiable risk factors account for 60% of AF incidence.^{10,11} Prevention is considered the highest quality intervention for AF,¹¹ and lifestyle modifications in the form of weight loss, smoking cessation, and control of DM, cholesterol, and HTN have been identified as possible targets.^{10,11}

With documented cardiovascular, cardioprotective, neuroprotective, cognitive, and anti-inflammatory benefits, chocolate is a possible target for primary prevention of AF. However, not all chocolate is created equal. In the European Union, milk

chocolate contains a minimum of 30% cocoa solids and dark chocolate contains a minimum of 43%, but the respective values in America are only 10% and 35%. Even though the participants in the Danish study consumed mostly milk chocolate, it contained a significantly higher dose of cocoa flavonoids than American chocolate. Cocoa flavonoids are responsible for the benefits of chocolate and excess milk or sugar may reduce bioavailability and efficacy.^{5,12}

This prospective cohort study showed that subjects who consumed chocolate on a weekly basis had the lowest risk of incidental AF, with the lowest HR for men at 2-6 servings per week and the lowest HR for women at 1 serving/week. The data presented in the original article appear to show a nonlinear, U-shaped dose response between chocolate intake and HRs, suggesting that there is an ideal dose for different individuals and that the effect disappears at extreme doses. The fact that a small amount of chocolate intake (1 ounce per week in women) had an effect is not atypical of the health impact of many dietary substances. Thus, it appears a little bit of good quality chocolate can go a long way.

The strengths of this study were the large sample size, detailed data on diet, and factors potentially related to AF, multivariate analysis, and almost complete follow-up. These patients were considered to be relatively healthy when compared to patients in similar studies that did not find significant associations, suggesting that results may not be generalizable to all patients.^{13,14,15} Indeed, the Danish population is white and very homogeneous compared to other European nations, and this cohort was healthier than others. Perhaps this reduced complexities and confounders associated with comorbidities and enabled the authors to detect a small effect due to chocolate.

The researchers acknowledged that they did not have information on silent AF, elective direct current cardioversions or AF reported in outpatient clinics, or emergency department visits and that the incidence of AF may have been underestimated. This study is weakened by the lack of adjustment for socioeconomic status, exercise, renal disease, and sleep apnea. Lower socioeconomic status in the United States is associated with reduced access to healthcare, higher morbidities, and poorer food choices, but perhaps this is not the case in Denmark. Renal disease and sleep apnea are associated with AF, and this may have affected the confidence intervals of the results if included in the multivariate analysis.

The sharpest criticism of this study is that chocolate consumers were healthier at baseline and had higher education levels, which may be associated with improved health habits and health status. Another counterintuitive consideration is the higher calorie intake of those participants who also consumed more chocolate than others. In the Danish study, the number of daily calories and the proportion of calories from chocolate increased with higher amounts of chocolate intake, but the BMI actually trended lower with more chocolate consumption. This effect also was observed in both Swedish cohorts,¹⁶ where subjects reporting higher intake of calories and chocolate showed incremental reductions in BMI and incremental increases in educational attainment.

Regular chocolate consumption appears to protect adults, men more than women, with few comorbidities, although appropriate dosing would have to be determined on an individual basis or via an intervention trial. Integration of chocolate into diets reasonably can start in older youths for whom high-quality chocolate with significant flavonoid content may be a better choice than a doughnut. Not only can chocolate potentially reduce the incidence of AF, but chocolate consumption is associated with reductions in other comorbidities associated with AF and aging, such as cognitive decline and heart failure. For these reasons, chocolate may be a positive addition to healthy lifestyle both as preventive and modulatory therapy of AF. While awaiting an interventional trial, we can tell patients who like chocolate that snacking on small amounts may be beneficial. ■

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PAIN

ABSTRACT & COMMENTARY

Acupuncture for Pain Control in the Emergency Department

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: In this study, researchers treated pain in the emergency department with acupuncture alone, acupuncture with conventional medication, or medication alone. They found acute efficacy was similar, although not optimal, for all modalities.

SOURCE: Cohen MM, Smit V, Andrianopoulos N, et al. Acupuncture for analgesia in the emergency department: A multicentre, randomised, equivalence and non-inferiority trial. *Med J Aust* 2017;206:494-499.

By nature, pain is a subjective and individual experience. It also is one of the most common presenting complaints in emergency departments (EDs) worldwide.² The term oligoanalgesia, defined as undertreatment of pain, emerged in the medical literature in a landmark 1989 paper in which it was described as a major concern in acute settings.³ In subsequent years, efforts to measure and quantify, treat, contain, and manage pain rose to the forefront. The opioid crisis and cautions regarding dispensing narcotic pain medications have uncovered layers of complexity involved in the treatment of pain. Today, despite extensive knowledge and medical advances, pain continues to be treated less than adequately in most ED settings.⁴

Recognizing the challenges of treating acute pain in EDs and knowing that acupuncture is used to address pain in many outpatient settings, Cohen et al designed a study to determine if acupuncture alone or in combination with conventional medication was at least as effective as medication alone in addressing acute pain in the ED. The authors examined pain relief effectiveness for migraine, lower back pain, or ankle sprain within one hour after presentation to the ED.

Notably, this was both an equivalence and a noninferiority study. Equivalence studies are used most often to demonstrate that differences between the treatments are not large in either direction (more or less efficacious), while noninferiority studies are used more often to demonstrate that the intervention is not worse than standard treatment.⁵ In this study, equivalence was examined between acupuncture-only and pharmacotherapy-only arms; noninferiority was examined when comparing the combined treatment (medication plus acupuncture) with pharmacotherapy only and with acupuncture only. There was no placebo arm because of ethical constraints.

Pharmacotherapy was delivered via a protocol based on national guidelines and included first- and second-line agents. The protocol included the following as a first step for each diagnosis: nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (400 mg), acetaminophen with or without codeine (500 to 1,000 mg paracetamol), or tramadol (50 to 100 mg). Specific interventions for each diagnosis included diazepam (5 mg) for lower back pain and metoclopramide for nausea associated with migraine. Rescue medication, including opiates for additional pain control, was administered to any participant at any time

Summary Points

- The authors of this multicenter Australian study sought to determine if acupuncture is at least as effective as conventional pharmacotherapy for acute pain relief in patients with low back pain, migraine, or ankle sprain in the emergency department (ED).
- They randomized 528 patients presenting with one of these complaints to receive either acupuncture alone, acupuncture plus pharmacotherapy, or pharmacotherapy alone.
- At one hour, acupuncture alone and acupuncture combined with medication were as effective in managing pain from acute ankle sprain and low back injury as pharmacotherapy alone. These modalities were not as effective as pharmacotherapy alone for migraine.
- None of the interventions were enough for full pain relief for the majority of participants at one hour post-admission. However, 48 hours after the ED visit, treatment satisfaction for the acupuncture and acupuncture plus pharmacotherapy groups increased from earlier measurements more than the pharmacotherapy group alone.

(regardless of group) if the provider deemed it necessary. Acupuncture was delivered in a standardized fashion with some individualization permitted. All acupuncturists were certified; four geographically diverse hospitals were selected for the study, so multiple acupuncturists were involved.

Pain was evaluated via a 10-point verbal numerical rating scale (VNRS), with a minimum score of 4 needed to qualify for the study. Pain scores were recorded hourly until discharge. Follow-up phone calls assessed pain up to 60 hours' post discharge. Pain relief to a score of < 4 was considered clinically relevant, while dropping a score > 2 points was considered statistically significant. According to the authors, a difference of at least 1.5 VNRS units between groups was clinically significant and indicated nonequivalence.

The authors identified several secondary outcome measures, including level of functional impairment at 48 hours after discharge, use of rescue

medication, adverse events, acceptability of treatment, and overall use of health resources.

Of 1,964 patients assessed, 528 eligible patients were randomized into one of the three treatment arms. Eligibility criteria included age (older than 18 years of age), ability and willingness to provide consent, and absence of acute major trauma or suspected infection.

Tables 1 and 2 review the number of participants for each diagnosis and each treatment arm. Treatment arms were randomized within each diagnosis. Note that treatment group percentages remained consistent throughout the study. For example, 31.4% of total patients presented with ankle pain and 31% of the total patients receiving any one of the three interventions presented with ankle pain. See Table 3 for select outcomes.

The acupuncture-only group received significantly more rescue medication. (See Table 4.) Satisfaction with treatment increased for all interventions from one hour to 48 hours after admission. Willingness to repeat the treatment increased from one hour to 48 hours after admission for the combined group and the acupuncture-only group. (See Table 4.) About 50% of participants in each treatment arm had an adverse event associated with the intervention. There was no statistical difference in this area among the treatment groups, and no further information was provided delineating the specific adverse events.

■ COMMENTARY

These results are best understood by looking closely at the context, setting, and goals of the study. The ethical constraints involved in randomizing treatment in the high-stakes, fast-moving ED setting presents barriers to design. Cohen et al explained that these barriers led to the use of equivalence and noninferiority parameters rather than a traditional randomized, controlled study. Yet, this design presents several challenges in interpretation. For example, did interaction with the acupuncturist influence pain relief? Would placebo medication combined with acupuncture have been as effective as conventional medication and acupuncture? It is important to know the answers to these questions before creating definitive treatment recommendations. Conclusions drawn from this study are limited to the parameters of equivalence and noninferiority.

Additionally, ethical concerns allowed the use of rescue medication at any point in the study at the discretion of the treating provider. A full 25%

Table 1: Number of Participants per Diagnosis

Diagnosis	Number of patients
Low back pain	270 patients (51.2%)
Ankle sprain	166 patients (31.4%)
Migraine	92 patients (17.4%)

of the acupuncture-only group received rescue medication during the first hour after admission to the ED (compared with 19% of the overall group; $P=0.016$.) It is not clear how quickly acupuncture or any of the studied interventions were administered during that first hour. The use of rescue medication essentially moves a significant portion of the group out of acupuncture-only and into the combined group, but presumably with a different algorithm or process than the members of the combined intervention group (who received medication on a predetermined schedule.) Clearly, pain management had to be achieved. However, it also is true that it is more difficult to control pain on a “prn” basis, and different providers will have varying biases and thresholds for intervention. These factors influenced the standardization of methodology in this study and lead to questions about the results.

Complicating matters further, Cohen et al chose to include three diagnoses and four settings. This allowed the study to gain strength from diversity of population as well as potential applicability to a variety of conditions. On the other hand, geographical diversity sacrificed control over specific providers. Given the subjective nature of pain, the specific ED provider and variations in the acupuncturist’s skill may play a role in the patients’ experience of pain; the extent or effect of this cannot be determined by this study.

Looking at three different diagnoses opened the study to more participants. Although it is true that equivalence studies are more powerful as the number of participants increases, the study is most credible when the diagnoses are looked at individually rather than grouped. Looking at individual diagnoses decreases the number of subjects and the power of the study to detect subtle but significant differences in results. Cohen et al acknowledged that the relatively low number of participants in the migraine group (91, or 17% of the total) may have affected results. A higher number of patients with migraine may have shifted the grouped results

Table 2: Number of Participants per Diagnosis

	Acupuncture only 177 patients	Acupuncture plus psychopharmacology 178 patients	Psychopharmacology only 173 patients
Low back pain	92 patients (51%)	91 patients (52%)	87 patients (50%)
Ankle sprain	54 patients (30%)	57 patients (32%)	55 patients (32%)
Migraine	31 patients (18%)	30 patients (17%)	31 patients (18%)

or may have narrowed the confidence limits within the migraine results. This is clearly an avenue for further exploration.

Although Cohen et al stated that satisfaction with treatment was a secondary goal of the study, these results are interesting and deserve a close look. Patients were contacted 48 hours after treatment and asked about their willingness to repeat the intervention. The percentage of participants who received acupuncture only or combined treatment and expressed a “definite yes” when asked about willingness to repeat increased from 47% at one-hour after ED admission to 61% 48 hours later for the acupuncture-only group and from 49% to 57% in the combined treatment group. When the pharmacotherapy-only participants were asked the same question, the “definite yes” response rate dropped from 57% at one-hour after admission to 52% 48 hours later. Although none of these results shows statistical significance, it is notable that willingness to repeat a treatment may change over time, the change may be toward more acceptance, and the shift may be influenced by a variety of factors. This is another area for future study and investigation.

Cohen et al noted that patients with an overall mean pain score of 6.7 one hour after ED admission reported that pain was not treated satisfactorily with any of the interventions. Additionally, they noted scores < 4 one-hour after admission (where < 4 is clinically relevant relief from pain) occurred in only 16% of the total group. Yet, 50% of participants felt comfortable enough one hour after admission to say they definitely would repeat the same treatment. This apparent contradiction may lead to questions if quantification of pain is enough to assess patient satisfaction or even comfort. It may be that for some patients, remaining with a degree of pain was preferable to experiencing further intervention or medication.

This study suggests several promising areas for future research as well as clinical applicability in

Table 3: Selected Outcomes**Equivalence testing (pharmacotherapy vs. acupuncture alone)**

- The migraine group alone demonstrated nonequivalence between treatments, with a mean difference in pain level between acupuncture and pharmacotherapy = 0.5 (favoring pharmacotherapy) and a relatively large confidence interval of 2.5.
- Both other diagnoses (low back pain and ankle sprain) demonstrated equivalence in pain reduction with both interventions.

Noninferiority testing (acupuncture only vs. combined therapy)

- The migraine group alone failed to demonstrate noninferiority, with a mean pain score difference between acupuncture and combined therapy of 1 (favoring combined therapy) and a relatively large confidence interval of 2.5. In this case, acupuncture appeared inferior to standard treatment.
- Both other diagnoses (low back pain and ankle sprain) demonstrated noninferiority in pain reduction with these interventions.

Noninferiority testing (acupuncture only vs. pharmacotherapy and combined treatment)

- The migraine group was alone in failing to demonstrate noninferiority, with a mean pain score difference between the groups of 0.5 (favoring pharmacotherapy and combined group) and a relatively large confidence interval of 2.
- Both other diagnoses (low back pain and ankle sprain) demonstrated noninferiority in pain reduction with these interventions

Pain measures in general

- All diagnoses: At one hour after admission to the ED, the decrease in mean pain score for all patients was 2.1 VDRS units. There was no statistically significant difference between any of the groups.
- All diagnoses: At one hour after admission to the ED, the mean pain score was 6.7. There was no statistically significant difference between any of the groups.

the interim. For example, the results of the largest diagnostic group (low back pain group; n = 270) are worth a second look. Acupuncture alone in an acute setting showed equivalence to conventional psychopharmacology, which can be useful to know

Table 4: Rescue Therapy Needs, Willingness to Repeat Therapy, and Adverse Effects for the Different Treatment Groups

	Rescue therapy within one hour of presentation (P = 0.016)	Rescue therapy any point after one hour of presentation (P = 0.008)	Willingness to repeat at one hour post presentation (definitely yes) (P = 0.015)	Willingness to repeat at 48 hours post presentation (definitely yes) (P = 0.64)	Adverse events
All participants	19% (98 participants)	8.5 % (45 participants)	50.7% (259 participants)	56.6% (237 participants)	51.7% (216 participants)
Acupuncture only	25% (45 participants)	14% (24 participants)	47% (81 participants)	61% (88 participants)	51% (73 participants)
Combined treatment	15% (27 participants)	4.5% (8 participants)	49% (86 participants)	57% (80 participants)	50 % (71 participants)
Medication only	15% (26 participants)	7.5% (13 participants)	57% (92 participants)	52 % (69 participants)	54% (72 participants)
Bold = important findings					

when offering treatment to this population. Costs and availability of acupuncture in local EDs may be a temporary barrier that can be overcome with education, more studies, and continued efforts toward insurance reimbursement models.

This study reminds providers to be cognizant of the subjective nature of pain and especially to note that for some, patient satisfaction does not require complete pain control. In addition, although some of the methodologic shortcomings detract from the results, it is clear that many patients (at least in this population) are willing to consider acupuncture as a treatment for pain in the ED. More than 50% of these patients stated willingness to repeat this intervention. These findings alone are

compelling and deserve a thought when considering pain control in acute settings. ■

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INFERTILITY

ABSTRACT & COMMENTARY

Acupuncture as Adjunct Therapy for Infertility in Polycystic Ovary Syndrome

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Dr. Lindgren and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: Acupuncture as an adjunctive therapy for treating infertility in Chinese women with polycystic ovary syndrome receiving clomiphene citrate or placebo offered no benefit over sham acupuncture.

SOURCE: Wu X-K, Stener-Victorin E, Kuang H-Y, et al. Effect of acupuncture and clomiphene in Chinese women with polycystic ovary syndrome. *JAMA* 2017;317:2502-2514.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that causes infertility in women of reproductive age.¹ It is characterized by ovulatory dysfunction, excess androgen production and associated manifestations, and polycystic ovaries. The etiology remains unknown. Prevalence estimates vary and range from 2.2% to as high as 26%, depending on which diagnostic inclusion criteria are used.¹ Although clomiphene citrate is a first-line treatment for anovulation and infertility related to PCOS,² investigations of alternative methods to treat infertility in women with PCOS have been ongoing. A Cochrane Review found insufficient evidence to support the use of acupuncture for treatment of ovulation disorders in women with PCOS, despite some individual trials that demonstrated acupuncture as effective for ovulation induction.³ For example, investigators in one study concluded that higher ovulation frequency occurred in women with PCOS receiving repeated acupuncture treatments.⁴ Studies showing benefit have had methodologic flaws or have been underpowered, preventing sufficient statistically significant evidence to change clinical management. Wu et al devised an adequately powered trial to investigate the effects of acupuncture as an adjunct therapy with clomiphene on live birth rates in Chinese women with PCOS and infertility.

The PCOS Acupuncture and Clomiphene Trial (PCOSAct) was a randomized, placebo-controlled, multicenter trial that included patients at 21 sites in the National Clinical Trial Base of Chinese Medicine in Gynecology from Mainland China. This 2 × 2 factorial trial was designed to examine the effects of active or sham acupuncture in combination with clomiphene or placebo to determine the effects on live births in Chinese women diagnosed with PCOS. Lacking strong preliminary data on live birth after acupuncture, 10% was chosen as the minimal clinically detectable difference likely to change clinical practice.

The investigators calculated that 1,000 women would need to be enrolled in the study based on

the following assumptions: a 25% live birth rate with both active interventions; a 15% live birth rate with one active and one control intervention; a 5% live birth rate with both control interventions; an 80% power at a significance level of $P \leq 0.05$; and a 10% dropout rate. The investigators screened 4,645 women with PCOS and determined 1,000 participants were eligible for inclusion. These participants were randomly assigned and placed in a 1:1:1:1 ratio into four intervention groups: active acupuncture plus clomiphene, sham acupuncture plus clomiphene, active acupuncture plus placebo, and sham acupuncture plus placebo. The assignments were double-blinded to everyone except the acupuncturists, who knew if they were delivering active or sham acupuncture.

Both active and sham acupuncture treatments were administered for 30 minutes twice a week, for a maximum of 32 treatments. Active acupuncture points were located in the abdominal and leg muscles associated with known autonomic innervation of the ovaries and the uterus according to traditional Chinese medicine, as well as in the hands and head. Manual and low-frequency electrical stimulation of the needles was applied in the active acupuncture treatments. In the sham acupuncture protocol, four needles were inserted superficially (less than 5 mm) without manual stimulation, one in each shoulder and upper arm at non-acupuncture points. The four needles were attached to electrodes and the acupuncturist simulated switching on the stimulator, mimicking the active acupuncture protocol, although no electrical stimulation actually was delivered.

For the medication protocol, subjects were given initial oral doses of clomiphene 50 mg or placebo between days 3 and 7 of the menstrual cycle. In patients with irregular menses and without recent menstruation, the researchers induced withdrawal bleeding with medroxyprogesterone acetate (5 mg/d) for 10 days. These patients also took clomiphene or placebo between days 3 and 7 of active bleeding. Doses of oral medication or placebo

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Table 1: Primary Outcome Data Comparing Clomiphene/Placebo With Acupuncture/Sham Acupuncture – Live Births

Number of live births (% live births)					
Clomiphene citrate			Placebo		
+ ACU n = 235	+ sACU n = 236	Total n = 471	+ ACU n = 223	+ sACU n = 232	Total n = 455
69 (29.4%)	66 (28.0%)	135 (28.7%)	31 (13.9%)	39 (16.8%)	70 (15.4%)
Absolute differences (95% CI)					
Effect of acupuncture			Effect of clomiphene		
+ CC	+ PC	Overall	+ ACU	+ sACU	Overall
1.4 (-6.8 to 9.6)	-2.9 (-9.5 to 3.7)	-0.6 (-5.9 to 4.7)	15.5 (8.1 to 22.8)	11.2 (3.7 to 18.6)	13.3 (8.0 to 18.5)
CC: clomiphene citrate; PC: placebo; ACU: active acupuncture; sACU: control (sham) acupuncture					
Source: Wu X-K, Stener-Victorin E, Kuang H-Y, et al. Effect of acupuncture and clomiphene in Chinese women with polycystic ovary syndrome. <i>JAMA</i> 2017;317:2502-2514.					

were increased by one pill in the absence of ovulation or maintained in the presence of ovulation. The maximum dosage did not exceed 150 mg per day or 750 mg per cycle. In the absence of conception, the protocol was repeated for a maximum of four menstrual cycles. Patients were instructed to have regular intercourse every two to three days, and pregnancy and ovulation were ascertained by weekly monitoring of urinary human chorionic gonadotropin and serum progesterone levels. Pregnant patients were followed within the study with ultrasonography every two weeks until fetal heart motion was visible, then referred for routine obstetric care. Birth outcomes for these patients were obtained from their obstetrical records.

The primary outcome was live birth, defined by the authors as 20 weeks' gestation or later. See Table 1 for a summary of results. There were 69 live births (29.4%) in 235 patients receiving active acupuncture plus clomiphene, 66 (28.0%) in 236 patients with sham acupuncture plus clomiphene, 31 (13.9%) in 223 patients with active acupuncture plus placebo, and 39 (16.8%) in 232 patients with sham acupuncture plus placebo. Since no significant effect was noted on live births between clomiphene with and without active acupuncture ($P = 0.39$), the authors examined the main effects of clomiphene and active acupuncture. Clomiphene treatment was associated with significantly higher live birth rates than placebo treatment: 135 of 471 (28.7%) for clomiphene vs. 70 of 455

(15.4%) for placebo, a difference of 13.3% (95% confidence interval [CI], 8.0-18.5%). The live birth rate was not significantly different between the groups treated with active and sham acupuncture: 100 of 458 (21.8%) for active acupuncture vs. 105 of 468 (22.4%) for sham acupuncture, a difference of -0.6% (95% CI, -5.9% to 4.7%). Adverse events also were examined, as were quality-of-life scores using standard instruments such as the SF-36. Bruising at the needle placement sites and incident diarrhea were significantly higher in the active acupuncture groups compared to the sham acupuncture groups. (See Table 2.)

These results show that among Chinese women with PCOS, the use of acupuncture with or without clomiphene does not increase live birth rates. These results show that actual and sham acupuncture, with or without clomiphene, had similar, nonsignificant effects on the rates of live births in Chinese women with PCOS. The authors concluded that these findings do not support acupuncture as an infertility treatment for Chinese women with PCOS.

■ COMMENTARY

Although it is not uncommon for infertility centers to offer acupuncture to patients, especially those seeking assisted reproduction with in vitro fertilization, evidence of efficacy for increasing live births has not been shown.⁵ This is another study that fails to support acupuncture for improving

Table 2: Statistically Significant Side Effects: Active Acupuncture vs. Sham Acupuncture

Side effect	Active acupuncture n/total (%)	Sham acupuncture n/total (%)	Difference (95% confidence interval)
Bruising at needle insertion site	37/500 (7.4%)	9/500 (1.8%)	5.6% (3.0-8.2%)
Diarrhea	25/500 (5.0%)	5/500 (1.0%)	3.4% (1.2-5.6%)

fertility and live birth outcomes in a specific patient population plagued by ovulatory dysfunction and low fertility. On the other hand, this study bolsters existing evidence supporting clomiphene as first-line pharmacologic therapy for improving live birth rates in infertile women with PCOS.²

PCOS management strategies include diet, exercise, weight loss when needed, and a variety of medications to manage insulin resistance and other symptoms.³ When clomiphene fails in patients with PCOS, strategies to improve fertility also include improving insulin resistance, mainly with metformin.² This practice suggests that insulin resistance may contribute to infertility in these patients, and it begs whether integrative therapies aimed at reducing insulin resistance might be helpful, including acupuncture. Further, the authors suggested that the standardized acupuncture intervention in this study, aimed solely at inducing ovulation, would be atypical of traditional acupuncture treatment, which characteristically is individualized to a specific patient rather than a specific medical condition.

The strengths of this study include its design and methodology as well as its size. There were similar withdrawal rates across all groups and high adherence rates among participants. Since the study only involved Chinese women in China, the results should not be generalized to women of other ethnic groups or geographic locations. The authors concluded that their findings do not support acupuncture as treatment for infertility due to PCOS.

However, without a true control group receiving neither treatment or placebo, one could argue that true and sham acupuncture both improved fertility rates, but less so than clomiphene.

Although acupuncture treatment in this study resulted in increased rates of diarrhea and bruising at needle sites, these side effects, though undesirable, occurred relatively infrequently. Further, the authors cited a clear placebo effect from both actual and sham acupuncture in increasing live birth rates compared to a previous study using physical therapy as a control intervention. Acupuncture is a safe intervention and few options for treating PCOS-related infertility exist. Despite the absence of evidence of efficacy suggested by this study, there are enough lingering questions to suggest that PCOS patients who wish to pursue individualized acupuncture as an adjunct therapy infertility should be informed, but not discouraged, assuming cost of treatment is not a burden. ■

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CME QUESTIONS

1. **In a Danish prospective cohort study, chocolate consumption in women showed the strongest inverse relationship with incident atrial fibrillation at which of the following doses?**
 - a. 1 serving per day
 - b. 1 serving per week
 - c. 2 servings per day
 - d. 6 servings per week
2. **Which of the following is true about acupuncture for pain control in the emergency department (ED)?**
 - a. Acupuncture is much more accepted in community clinic settings than in acute EDs, except in patients with a history of acupuncture treatments prior to the ED visit.
 - b. Acupuncture alone was equivalent in efficacy to medication alone for treatment of low back pain and ankle sprain in the ED, but these patients also received significantly more relief medication than the patients receiving medication alone.
 - c. Acupuncture alone and acupuncture combined with medication showed equivalent efficacy to pharmacotherapy alone for treatment of low back pain, ankle sprain, and migraine in the ED.
 - d. Acupuncture was widely accepted in the ED setting and preferred by many patients as an alternative to conventional pharmacotherapy for pain control, except in patients with migraine.
3. **In the PCOS Acupuncture and Clomiphene Trial (PCOSAct), which of the following was noted as a statistically significant side effect of active acupuncture compared to sham acupuncture?**
 - a. Headache
 - b. Diarrhea
 - c. Skin discoloration
 - d. Myalgia

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

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