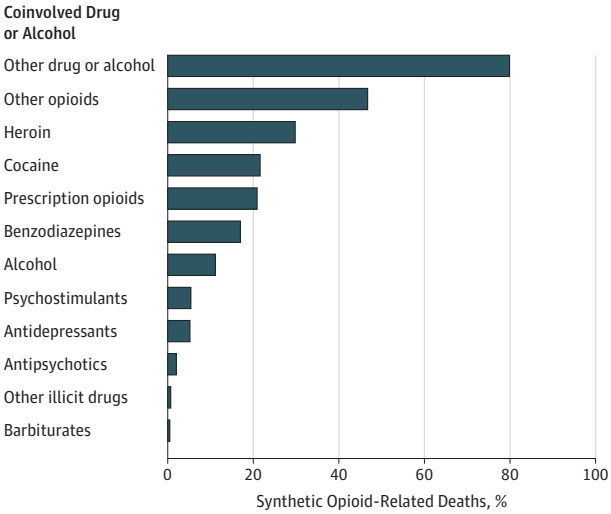
Figure. Percentage of Synthetic Opioid-Related Overdose Deaths Involving Illicit or Psychotherapeutic Drugs or Alcohol in the United States, 2016




[a] Deaths are not mutually exclusive. Percentages sum to more than 100%.

*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Jones.
*Critical revision of the manuscript for important intellectual content:* Compton, Einstein.
*Statistical analysis:* Jones.
*Supervision:* Jones.

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**Disclaimer:** The findings and conclusions of this study are those of the authors and do not necessarily reflect the views of the Substance Abuse and Mental Health Services Administration or the National Institute on Drug Abuse of the National Institutes of Health.

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COMMENT & RESPONSE

## Cervical Pessary and Spontaneous Preterm Birth

**To the Editor** Dr Saccone and colleagues[1] conducted a randomized clinical trial on the effect of a cervical pessary in women with singleton pregnancies and short cervical length and found that a pessary compared with no pessary resulted in a lower rate of spontaneous preterm birth. The authors achieved exactly their trial registry-planned sample size of 300, with 100% follow-up and 100% adherence to treatment allocation in both groups. The adherence seems implausible, as my patients commonly request removal for discomfort or other reasons.

In addition, exactly equal numbers of 150 women were randomized to each group. Women were "randomized by a web-based system ... implemented by use of a central telephone number." According to the protocol, http://www.randomization.com was used, and this can produce exactly 150 per group if 25 randomized blocks each of size 2, 4, and 6 are entered. But "randomization was stratified by cervical length (≤20 mm or >20 mm to ≤25 mm)," so separate random sequences must have been created for each stratum. For example, in the stratum with cervical length more than 20 mm (Table 1 in the article), 17 women (150 minus 133) were recruited in the pessary group and 25 (150 minus 125) in the control group. This imbalance of 8 is impossible with balanced blocks of 2, 4, and 6. At most, the imbalance would be 3, if recruitment ended halfway through a block of 6 with 3 same allocations in a row.

There is also a problem with the Kaplan-Meier analysis presented in the article's Figure 2A (all delivery types) and Figure 2B (spontaneous delivery only). The curves differ, albeit not by much, but the numbers at risk at each gestation were identical. Could one of the sets of numbers at risk be wrong?

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**In Reply** As Dr Thornton suggests, one of the strengths of our trial was the 100% follow-up and the 100% adherence to the treatment allocation in the pessary group. These high rates were obtained because all women included in the trial delivered at the study institution. Moreover, included women were extensively informed by the research staff about the risk of preterm delivery. We strongly believe that all women would keep a cervical pessary if clinicians clearly explained to them that the benefits of having a healthy full-term infant outweigh the risk of having discomfort. Indeed, almost all women in the pessary group experienced some adverse effects (86.7% had vaginal discharge and 3.3% had pelvic discomfort) but none of them had the device removed. Effective physician-patient communication is a central clinical function in building a therapeutic relationship.[1]

Regarding the randomization, women were randomized by a web-based system (http://www.randomization.com) using random blocks of 2, 4, and 6 to receive the pessary or no pessary. Randomization was stratified by cervical length, and separate randomization sequences were created by an independent statistician. However, there was an error in the article. The randomization strata were less than 20 mm and equal or greater than 20 mm to equal or less than 25 mm, not equal or less than 20 mm and greater than 20 mm to equal or less than 25 mm as stated. Using the erroneous cutoff would lead to imbalance between the groups, as Thornton suggested. However, with the correct cutoff, no imbalance was noticed, with 125 women with a cervical length less than 20 mm and 25 women with a cervical length equal or greater than 20 mm to equal or less than 25 mm in each group. The number of women with a cervical length equal or less than 20 mm in Table 1 was correct, as equal or less than 20 mm was the cutoff used for vaginal progesterone therapy, as recommended by guidelines.[2] The article has been corrected online and we apologize for any confusion this may have caused.

Regarding the Kaplan-Meier curves, the numbers of women at risk, reported in Figure 2, were the total number of randomized women minus the number of women who already delivered, regardless of whether they had iatrogenic or spontaneous preterm birth. Therefore, the numbers of women at risk are the same for both curves.

The benefits of the pessary shown in our trial could be explained by the high treatment adherence compared with other trials. There are several ongoing trials evaluating the efficacy of cervical pessary in prevention of preterm birth, and there are plans for an individual patient data meta-analysis that will include our data. The meta-analysis will update prior reviews[3,4] and hopefully will clarify the effect of cervical pessary in prevention of preterm birth.

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**Conflict of Interest Disclosures:** Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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## Quality of Life in Patients With Glioblastoma Treated With Tumor-Treating Fields

**To the Editor** In a multisite, randomized, phase 3, clinical trial, Dr Stupp and colleagues[1] demonstrated a modest benefit for patients newly diagnosed with glioblastoma treated with tumor-treating fields (TTFields) and temozolomide vs temozolomide alone in progression-free survival (7.1 months for TTFields plus temozolomide vs 4 months for temozolomide alone) and overall survival (20.9 months for TTFields plus temozolomide vs 16 months for temozolomide alone). The authors should justify the current cost of the device ($20 000 per month) and also the discuss the effect on quality of life for both the patients (shaving their head) and family when patients wear the TTFields device 18 hours a day.

Cognitive (Mini-Mental State Examination) and functional (Karnofsky performance score) metrics were included in their analysis, but the use of standardized, health-related quality-of-life scores (such as the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire and its brain-specific module) were not mentioned. Tumor-treating fields plus temozolomide compared with temozolomide alone showed no significant differences in time to a sustained 6-point decline in the Mini-Mental State Examination score.[1] Standardized health-related quality-of-life scores take into account emotional, social, and role functioning.[2] An interim analysis conducted on the first 315 randomized patients did not show significant differences for any of the functional scales on either questionnaire in either treatment group.[2] A larger analysis incorporating 92% of the patients noted that 42% of patients had not completed the questionnaires at the 1-year follow-up.[3] The physical and emotional burden of shaving one's head while wearing the device 18 hours a day (including while sleeping) cannot be underestimated for both patient and family members. In fact, it is the partner, friend, or family member who must change the adhesives, administer scalp care, and adjust the TTFields device when it malfunctions, even in the middle of the night.

Other trials, perhaps with less significant psychiatric implications, may be better suited for patients with newly diagnosed glioblastoma. For example, a phase 3 trial (CeTeg/NOA-09) showed that the combination of lomustine and temozolomide significantly improved median overall survival (37.9 months with lomustine, temozolomide, and radiotherapy vs 31.4 months with temozolomide and radiotherapy alone) in patients with the $O^6$-methylguanine-DNA methyltransferase (*MGMT*) promoter.[4]

In sum, although TTFields plus temozolomide provides an interesting and innovative treatment for newly diagnosed glioblastoma, a better understanding of the effect on patient and family quality of life needs to be assessed, especially to justify TTField's increased economic and emotional burden.

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