Treatment for patients with newly diagnosed glioblastoma–reply

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the cumulative risk for a suicide attempt or completion over the next year 10-fold and 100-fold, respectively.[2] Self-report is more sensitive for detecting suicidal ideation than clinician interviews.[3] Depressed residents, evaluated by the HANDS inventory (Harvard Department of Psychiatry/National Depression Screening Day Scale), make 6.2 times as many medication errors per month.[4] Underscoring the significance of depression data from surveys, clinical guidelines explicitly support their use in assessing and treating depression.[5]

In the article, we provided a table of the sensitivities and specificities of inventories included in the meta-analysis to allow readers to judge the degree to which these estimates reflected true MDD prevalence. We invite Levis and colleagues to apply these parameters to the instrument-specific prevalence estimates in Figure 3 in the article, as doing so demonstrates that MDD among residents is several-fold higher than in the general population.

The methods used by some primary studies in our meta-analysis have limitations. Future studies should incorporate well-validated assessment tools, longitudinal follow-up, and large sample sizes. This discussion, however, should not distract from the conclusion that resident depression and depressive symptoms are alarmingly high. The relevant question is not whether they are high but rather why they are high. The response to this question will have an important effect on residents and their patients.

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Treatment for Patients With Newly Diagnosed Glioblastoma

To the Editor Dr Stupp and colleagues[1] reported on the combined use of temozolomide and tumor-treating fields (TTFields) compared with temozolomide alone as adjuvant therapy in patients with newly diagnosed glioblastoma. The study of 315 patients demonstrated improvement in progression-free survival (3.1 months) and overall survival (4.9 months) in the TTFields-treated cohort (210 patients). The question is whether this study, an interim analysis of the total study population of 695 patients, is sufficiently compelling to change current therapies for glioblastoma.

Barriers to use are manifold and include difficulty in use of the device, cost of the device, the failure of TTFields for recurrent glioblastoma, the potential palliative care effect afforded by use of TTFields, and the uncertain exact mechanism of action (as summarized in the accompanying Editorial[2]). As the device is currently configured, patients are required to shave their head twice per week, apply an adhesive electrode array covering nearly the entire scalp, and wear a 2.7-kg battery pack continuously for optimal benefit.

The conspicuity of the TTFields device makes any patient wearing it a subject of interest and curiosity. The cost of the device is approximately $20 000/mo. Because the TTFields treatment requires an external portable device, it is often not covered by insurers, potentially creating a significant financial burden on the patient's family. A previous trial of patients with recurrent glioblastoma designed to show superiority of TTFields compared with physician-determined best therapy was negative.[3]

Whether involvement by the TTFields team (eg, assisting in device set-up, familiarizing the family and patient with operation of the device, providing replacement equipment, and 24/7 telephone access) contributes to survival benefit by way of surrogate palliative care is unclear and a potential confounder.[4] Perhaps the greatest challenge to implementation of TTFields is acceptance by the neuro-oncology community (the clinicians primarily providing care for patients with glioblastoma).

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In Reply Tumor-treating fields are a novel approach to the treatment of cancer. In vitro and animal studies have demonstrated that the use of alternating electrical fields, at a

frequency specifically tuned to penetrate tumor cells, interferes with microtubule formation, proper localization of the cytokinetic contractile ring, and chromosomal segregation, leading to cell cycle arrest, apoptosis, and reduced clonogenic potential.[1-3] Little progress has been made in the treatment of glioblastoma over the last decade, yet our study demonstrated a significant improvement in both progression-free and overall survival in patients with glioblastoma.

Dr Chamberlain suggests the results we found with TTFields may be a placebo effect due to better palliative care. Medical follow-up was identical in both treatment groups. Although the patients treated with TTFields had access to a 24-hour hotline, it was intended for possible technical problems with the device. Once the first 2 to 3 weeks of treatment had passed, most patients became independent with the device, and intervention by the technician was limited to 1 visit per month to supply new materials, record the use of the device, and solve any technical problems.

The placebo effect is also thought to be an unlikely explanation based on the results of 2 large randomized trials comparing intensified maintenance therapy with either dose-dense temozolomide (21 d/mo vs 5 d/mo)[4] or the addition of cilengitide (requiring twice weekly visits to the chemotherapy suite for intravenous administration).[5] Improved outcomes were not observed in either trial with the more intensive treatment (hazard ratios for survival, 1.03 [P = .63] and 1.02 [P = .86], respectively).

Chamberlain points out that the device did not show superiority for recurrent disease[6] (which also applies for most other treatments used), thus contradicting the placebo hypothesis. In the recurrent setting, TTFields was used as a single modality in very advanced disease, rather than in combination with chemotherapy in newly diagnosed patients.

We consider the difficulty in using the device to be quite limited (the second-generation device weighs 1.3 kg), and the electrodes are hidden easily beneath a cap or a wig. It is up to the patient to decide whether the improvement in the 2-year survival rate by 50% (from 29% to 43%) is worth it. The cost of cancer treatments is a growing concern in all of oncology. The costs, albeit substantial, are in the range of many other cancer therapies.

Chamberlain speculated about resistance by the neuro-oncology community to accept the results of the trial. It is difficult to explain why open and critical scientific minds would refuse to integrate sound clinical trial results into practice, even if the results were unexpected, especially when better alternatives are in short supply. Although the results were interim, they were scrutinized for a best and worst case scenario, and it is unlikely that the final results will show a substantially different outcome.

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China's One-Child Policy

To the Editor Dr Hesketh and colleagues[1] provided a summary and critique of China's one-child policy, expressing skepticism that eliminating this policy will cause fertility rates in China to rebound. The authors delineated several positive aspects of the one-child policy. However, those apparent positives are mitigated by the corresponding costs associated with them.

The first positive aspect was the reduction of the total fertility rate, its resulting prevention of 400 million births, and the corresponding short-run demographic dividend. However, this is unlikely to create a demographic dividend in the long run.[2]

The second positive aspect, the reduction of female morbidity and mortality risk from fewer pregnancies, overlooked the morbidity and mortality risks associated with the lack of family support and higher incidence of loneliness in the elderly that having only 1 child could exacerbate.

The third positive aspect was the acceleration toward gender equality. How can a policy that resulted in the sex-selective abortion of millions of girls simply because they were identified as female, and that caused a gender imbalance and a corresponding market for trafficking young women, be viewed as accelerating a movement toward gender equality? As China implements its two-child policy, it remains to be seen whether the country will experience a more rapid convergence toward gender balance and whether other forms of child gender bias (unable to be manifested within 1-child families) will replicate the bias that continued to exist in the multichild households permitted by China.