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Postoperative Delirium—Amplifying the Confusion

To the Editor We read the article by Sieber et al[1] with great interest. Postoperative delirium (PD) is an increasing problem and one of the least well-understood problems today. Whether general anesthesia leads to PD that in turn leads to or unmasks dementia (Alzheimer disease) is the bigger question, as referred to in the Editorial accompanying this article.[2] Sieber et al[1] hereby fail to prospectively find an association of PD with depth of anesthesia. Within its limitations, on the one hand, this reassures us of the safety of use of anesthetics in older patients; on the other hand, this once again reinforces our belief that PD has a more complex etiopathology than we understand to date. Despite controlling for most factors (Table 1[1]), what stands out is the mean age in both groups was older than 80 years. Maybe this could have contributed to the lack of a difference in the primary end point, as most patients in similar studies were much younger (aged approximately 60 to 65 years).[3] Second, Sieber et al[1] studied a sedation protocol for nonelective low-risk surgery; what if the authors had studied an intermediate-risk or high-risk surgery, such as intraperitoneal or vascular surgery? Third, this article raises the same questions around PD: is it the type of anesthetic drug (eg, intravenous vs inhalational) or is it the patient phenotype and their individual anesthetic sensitivity[4] that determines the outcome, since even low anesthetic depth has been associated with delirium?[5] The results and scope of this study need to be interpreted and applied with extreme caution, as it may not apply to general anesthesia, longer surgical duration, more invasive or major surgical procedures, and even individual patient phenotype.

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Conflict of Interest Disclosures: None reported.

1. Sieber FE, Neufeld KJ, Gottschalk A, et al. Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: the STRIDE randomized clinical trial. *JAMA Surg*. 2018;153(11):987-995. doi:10.1001/jamasurg.2018.2602

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In Reply We appreciate the comments by Pal and understand the quandary in trying to generalize our study.[1] Pal's comments concerning age, surgery risk, type of anesthetic drug, or phenotype certainly point to the evidence that postoperative delirium is a complicated geriatric syndrome and that many factors weigh into its causation. Many of the factors mentioned should be the focus of future studies in this area to help enhance our understanding and improve management. From our study design, we cannot comment on surgical risk or other anesthetic drugs. However, in this randomized clinical trial, in an older population undergoing hip fracture repair, lighter propofol sedation was not found to decrease the incidence of postoperative delirium except in a subgroup of patients with lower comorbidity.[1] All of the modeling approaches for delirium analysis accounted for age. The data suggest, as does Pal, that patient phenotype, particularly underlying comorbid state, and clinical factors, such as depth of sedation, may play more complex roles in the risk of postoperative delirium than simply instilling their individual direct effects toward this complicated geriatric syndrome.

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1. Sieber FE, Neufeld KJ, Gottschalk A, et al. Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: the STRIDE randomized clinical trial. *JAMA Surg*. 2018;153(11):987-995. doi:10.1001/jamasurg.2018.2602

Gastroschisis and Autism—Dual Canaries in the Californian Coalmine

To the Editor We note the report on the gastroschisis incidence rising 3.1-fold from 1995 to 2012.[1] The 20-fold variation across California mirrors the 10-fold variation across Canada,[2] where the distribution pattern closely mirrored cannabis consump-

tion and from where a cannabis-adjusted odds ratio (OR) of 3.54 (95% CI, 2.22-5.63) has been reported.[3]

Several clues suggest cannabis is likely also involved in California. Statewide gastroschisis incidence rose 2.84-fold from 2005 to 2012, while last month cannabis use in northern California rose 2.56-fold from 8.41% to 21.55% from the periods 2006 to 2008 to 2014 to 2016 in the National Survey of Drug Use and Health (NSDUH). Combining the midrange county rates supplied in Figure 2A[1] with published birth, population, and NSDUH data, it can be shown that the gastroschisis rate increased in the NSDUH 1R northern 15 counties (OR, 2.33; 95% CI, 1.91-2.83) compared with the rest of the state for the whole period of 1995 to 2012.

Anderson et al[1] found rurality was a risk factor for cannabis use, which fits with the burgeoning cannabis industry. Timber production was a probable surrogate marker, and US National Parks are known to accommodate substantial cannabis plantations. Moreover, as various potent herbicides and rodenticides, including carbofuran, are used in commercial operations and contaminate the water table, these also need to be considered as novel indirect toxins.

Gastroschisis follows cannabis use in many places, including Australia, Canada, Mexico, North Carolina, and Washington. Mechanistically, this is consistent with the appearance of cannabinoid type 1 receptors on the omphal vitelline vessels from the ninth week of gestation and documented occurrence of cannabis arteritis.[4]

The real possibility clearly needs to be considered that the global rise in cannabis use may underlie the dramatic rise in gastroschisis in many locations. Indeed, since heart and brain defects, including anencephaly and brain impairments consistent with autistic deficits, are also well described in the congenital cannabis exposure literature together with Down syndrome, it may be that a wide variety of defects could be related to the budding industry.

The potential link with the autism spectrum, including cannabis-dependent, dose-related, and rampant neurexin-neurologin-mediated synaptic dehiscence, is of particular concern. The rapidly growing autism epidemic in Colorado is matched by an autism hotspot in the northern cannabis zone of California,[5] which has likely become even hotter since that study was conducted.

Careful substance-spatiotemporal analyses of positive and negative correlation are indicated to investigate causal relationships. The possibility of worldwide multiorgan cannabis-induced, cannabinoid type 1 receptor–mediated severe clinical teratology has not been widely canvassed.

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Conflict of Interest Disclosures: None reported.

1. Anderson JE, Cheng Y, Stephenson JT, Saadai P, Stark RA, Hirose S. Incidence of gastroschisis in California. *JAMA Surg*. 2018;153(11):1053-1055. doi:10.1001/jamasurg.2018.1744

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In Reply In their letter, Reece and Hulse suggest there may be a correlation between cannabis consumption and gastroschisis based on the high consumption of cannabis in counties where we have found high rates of gastroschisis. To be clear, Reece and Hulse are inaccurate in their statement that we "found rurality was a risk factor for cannabis use." Instead, we found higher rates of gastroschisis in rural counties.[1] In a follow-up study,[2] we found that fetal exposure to drugs other than alcohol, cocaine, narcotics, or hallucinogenics (odds ratio [OR], 3.27; 95% CI, 1.05-10.15; $P = .04$) and other noxious substances (OR, 2.02; 95% CI, 1.29-3.18; $P = .002$) increased the risk of gastroschisis in univariate analyses. The risk of combined exposure to other drugs and noxious substances persisted even when adjusting for rurality in a multivariate analysis (OR, 1.58; 95% CI, 1.01-2.49; $P = .005$). These drugs could include cannabis, among others, although this is impossible to determine, given the limitations of *International Classification of Diseases, Ninth Revision* coding used in this administrative database.

The detail in the new *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis codes will hopefully strengthen and refine observational studies that use administrative data. In the future, big data, including merging biomedical, epidemiological, and sociological data, may also offer more sophisticated analyses to identify risk factors associated with congenital malformations.

In the meantime, there are clearly geographical distributions of gastroschisis, which may correspond to geographic variability in drug exposures, including potentially marijuana and/or methamphetamine. However, we must be vigilant to avoid making claims about causation when only correlations exist. With the legalization of marijuana in California and other states, we should make greater commitments to studying its effects on fetal development.

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Conflict of Interest Disclosures: None reported.

1. Anderson JE, Cheng Y, Stephenson JT, Saadai P, Stark RA, Hirose S. Incidence of gastroschisis in California. *JAMA Surg*. 2018;153(11):1053-1055. doi:10.1001/jamasurg.2018.1744

2. Anderson JE, Galganski LA, Cheng Y, et al. Epidemiology of gastroschisis: a population-based study in California from 1995 to 2012. *J Pediatr Surg*. 2018;53(12):2399-2403. doi:10.1016/j.jpedsurg.2018.08.035

CORRECTION

Correction to Add Description of and Citation to Related Articles and Complete Description of Study Methods: In the Original Investigation titled "Association of O^6-Methylguanine-DNA Methyltransferase Protein Expression With Postoperative Prognosis and Adjuvant Chemotherapeutic Benefits Among Patients With Stage II or III Gastric Cancer,"[1] the authors had failed to provide citations to and description of the previously published and related 9 studies; a more complete explanation of the role of Shanghai Outdo Biotech Co, Ltd, in creating the tissue microarrays and evaluating the immunohistochemistry scores; and a better explanation of the rationale for use of R software, version 3.3.2, in the Abstract, Introduction, Methods, and eMethods 1 and eMethods 2 in the Supplement. These omissions did not affect the conclusions of the article. A Letter of Explanation[2] has been published that details the source of these errors. This article has been corrected online.

1. Cao Y, Liu H, Li H, et al. Association of O^6-methylguanine-DNA methyltransferase protein expression with postoperative prognosis and adjuvant chemotherapeutic benefits among patients with stage II or III gastric cancer. *JAMA Surg*. 2017;152(11):e173120. doi:10.1001/jamasurg.2017.3120

2. Xu J. Failure to cite related studies and report complete information on patients and tissue samples [published online February 6, 2019]. *JAMA Surg*. doi:10.1001/jamasurg.2018.5755

Transposed Data in a Table: In the Original Investigation titled "Effect of Incorporation of Pretreatment Serum Carcinoembryonic Antigen Levels Into AJCC Staging for Colon Cancer on 5-Year Survival," published in the August 2015 issue of *JAMA Surgery*,[1] 2 columns of data were transposed in a table. In Table 1, the information in the column headings was correct; however, the entire column of data for all patients should have appeared in the column for patients with C0 disease, and the column of data for patients with C0 disease should have appeared in the column for all patients. This article was corrected online.

1. Thirunavukarasu P, Talati C, Munjal S, Attwood K, Edge SB, Francescutti V. Effect of incorporation of pretreatment serum carcinoembryonic antigen levels into AJCC staging for colon cancer on 5-year survival. *JAMA Surg*. 2015;150(8):747-755. doi:10.1001/jamasurg.2015.0871

Error in Conflict of Interest Disclosures: In the Original Investigation titled "Association of Opioid Prescribing With Opioid Consumption After Surgery in Michigan,"[1] published online on November 7, 2018, a conflict of interest disclosure was missing at the time of publication. The conflict of interest disclosure section has been edited to add "Dr Howard recieves funding from the Blue Cross Blue Shield of Michigan Foundation." This article was corrected online.

1. Howard R, Fry B, Gunaseelan V, et al. Association of opioid prescribing with opioid consumption after surgery in Michigan. *JAMA Surg*. 2019;154(1):e184234. doi:10.1001/jamasurg.2018.4234

Errors in Results and Figure: The Original Investigation, "International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging System in Patients With Resected Pancreatic Cancer,"[1] published online October 3, 2018, was corrected to remove an errant "%" from the sentence "These findings result in an additive NRI of 0.38% and an absolute NRI of 28.6%." The sentence now reads "These findings result in an additive NRI of 0.38 and an absolute NRI of 28.6%." In addition, the label on the x-axis of both receiver operating characteristic curves in Figure 2 has been corrected to "1 − Specificity," instead of "Specificity."

1. van Roessel S, Kasumova GG, Verheij J, et al. International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer [published online October 3, 2018]. *JAMA Surg*. 2018;153(12):e183617. doi:10.1001/jamasurg.2018.3617

Errors in Author Affiliation and Funding/Support: In the Research Letter "US Emergency Department Encounters for Firearm Injuries According to Presentation at Trauma vs Nontrauma Centers,"[1] published online January 23, 2019, the corresponding author's second affiliation was corrected to replace "Yale–Drug Abuse, Addiction, and HIV Research Scholars Program" with "Yale–Drug Use, Addiction, and HIV Research Scholars Program." Also, the corresponding author's Funding/Support was corrected to replace "award T32HS000028" with "grant T32HL098054" and to include award K12DA033312-06 from the National Institute on Drug Abuse. This article has been corrected online.

1. Coupet E Jr, Huang Y, Delgado MK. US emergency department encounters for firearm injuries according to presentation at trauma vs nontrauma centers [published online January 23, 2019]. *JAMA Surg*. doi:10.1001/jamasurg.2018.4640

Error in Figure: In the Original Investigation titled "Reoperations After Bariatric Surgery in 26 Years of Follow-up of the Swedish Obese Subjects Study,"[1] published online on January 2, 2019, labels in Figure 2A were reversed. The curve depicting Corrections was labeled "Reversals" and vice versa. This article has been corrected.

1. Hjorth S, Näslund I, Andersson-Assarsson JC, et al. Reoperations after bariatric surgery in 26 years of follow-up of the Swedish Obese Subjects Study [published online January 2, 2019]. *JAMA Surg*. doi:10.1001/jamasurg.2018.5084