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Further Lessons in Pneumocystis Pneumonia Prophylaxis.

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Re-examining the Association Between "4/20" and Fatal Crashes—Doobie-ous Data?

To the Editor In an analysis published in a recent issue of *JAMA Internal Medicine*, Staples and Redelmeier[1] reported higher numbers of drivers involved in fatal motor vehicle crashes on April 20, the "counterculture holiday known as '4/20,'"[1(p569)] when compared with the corresponding day of the previous (April 13) and following (April 27) weeks. However, analyzing the number of drivers involved in crashes—rather than the number of crashes—inflates crash numbers (and absolute differences in comparative crash numbers) because the majority of crashes included in the Fatality Analysis Reporting System database[2] involved more than 1 vehicle. We were also concerned that the authors appeared to have aggregated data for the 2 control dates, which can create the impression of an effect when one does not exist. For example, the number of crashes could be exactly the same on April 20 and on April 13, but a 20% lower crash count on April 27 would give the impression of a 10% excess in crashes attributable to 4/20. Finally, the analysis as presented did not fully convey the longitudinal nature of the data or more recent evolutions in any observed effect.

We re-created the authors' primary analysis by using the number of fatal crashes reported by the Fatality Analysis Reporting System[2] (rather than the number of drivers involved in fatal crashes) occurring between 4:20 PM and 11:59 PM on April 13, April 20, and April 27 from 1992 through 2016. We also analyzed the data for the most recent years (2010 onward) separately.

When aggregating the control date data, our relative results were markedly similar to those of Staples and Redelmeier[1] (incident rate ratio [IRR], 1.10; 95% CI, 1.02-1.20), but the absolute difference between April 20 and the 2 control dates was approximately halved (0.4 crashes per hour vs 0.7 drivers involved in crashes per hour).

Disaggregating the control dates provided additional insights. When comparing the number of crashes for each study date over the study period, in some years the number of crashes on April 20 was quite similar to the number of crashes occurring on at least 1 of the control dates. The April 20 crash rate remained significantly higher than the April 13 crash rate (IRR, 1.12; 95% CI, 1.02-1.23) but was not significantly different from the April 27 crash rate (IRR, 1.09; 95% CI, 0.99-1.20). We also found that there was convergence of the data since approximately 2010—a time when attitudes toward and laws about marijuana were becoming more liberal. Since 2010 there has been no significant difference in the number of crashes occurring on April 20 when compared with the control dates, whether analyzed in the aggregate (IRR, 1.03; 95% CI, 0.87-1.21) or separately (compared with April 13: IRR, 0.98; 95% CI, 0.81-1.19; and compared with April 27: IRR, 1.08; 95% CI, 0.79-1.31).

Our analysis raises doubts about any contemporary association between 4/20 celebrations and fatal crash rates. It is possible that growing societal acceptance of marijuana use has blunted some of the motivation for or intensity of 4/20 counterculture celebrations. We do wholeheartedly agree with Staples and Redelmeier that "regulatory and enforcement strategies to curtail drugged driving"[1(p571)] are important as marijuana laws become more liberal. We would not, however, want readers to interpret the data as suggesting that liberalization of marijuana laws is associated with increased crashes—indeed, there are data to the contrary.[3]

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Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

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Further Lessons in *Pneumocystis* Pneumonia Prophylaxis

To the Editor We read with great interest the Teachable Moment by LoPiccolo and collegues[1] that was published in a recent issue of *JAMA Internal Medicine*. Although we found the article to be highly relevant, we are concerned that it understated the potential harms of *Pneumocystis* pneumonia (PCP) prophylaxis and overstated its potential benefits.

Specifically, the authors asserted that PCP prophylaxis with trimethoprim-sulfamethoxazole was "not associated with an increased rate of adverse events, despite prolonged duration of prophylaxis."[1(1107)] However, the risk of adverse events with use of trimethoprim-sulfamethoxazole remains meaningful—severe adverse events, including leukopenia, thrombocytopenia, or severe dermatological reactions, require permanent discontinuation in 3.1% of adults.[2] Rates of adverse events to second-line antibiotics are even higher.

Second, although the recent Cochrane review[2] recommended consideration of PCP prophylaxis in non-HIV immunocompromised patients when the risk of PCP is greater than 6.2% per person-year, opinions vary around which conditions or medications confer this level of risk.[3] For example, although risk for patients with solid organ transplants generally exceeds the threshold of 6.2% for PCP prophylaxis, risk for patients with rheumatic diseases, such as rheumatoid arthritis, do not.[4] More evidence is needed to guide personalized risk assessments for PCP, because risk depends on the combination of concurrent immunosuppressant drugs and underlying diagnosis. It is also possible that our current understanding of PCP infection risk does not take into account other important factors, such as patient-

level differences in drug metabolism or the burden of PCP in the community or treating clinic.[5]

Perhaps the most important lesson from this case is to acknowledge that there is equipoise around the use of PCP prophylaxis in many situations—and that such areas of equipoise may benefit most from shared decision making with patients.

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Disclaimer: The content of this letter is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality or the National Institutes of Health.

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2. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for *Pneumocystis* pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev*. 2014;(10):CD005590.

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In Reply We agree with Schmajuk and Yazdany that adverse events occur in a small fraction of patients using trimethoprim-sulfamethoxazole, as they pointed out in response to our recent Teachable Moment.[1] However, at doses used for *Pneumocystis* pneumonia (PCP) prophylaxis, the drug combination is generally well tolerated, and gastrointestinal and cutaneous adverse effects, such as nausea and rash, occur in only 3% to 5% of patients.[2,3] In HIV-uninfected patients, most of the adverse reactions (eg, nausea, vomiting, skin rash, pruritus) are not severe and resolve with discontinuation of the drug; this is in contrast to the 25% to 50% of HIV-infected patients who experience adverse effects (eg, neutropenia, anaphylaxis, toxic dermatologic reactions), which are more likely to be severe.[4,5] Hyperkalemia, which can be life-threatening, has most commonly occurred in HIV-infected patients receiving high doses (trimethoprim, 20 mg/kg/d, and sulfamethoxazole, 100 mg/kg/d) for PCP treatment.[4] Additionally, it is well known that the trimethoprim-sulfamethoxazole–induced creatinine increase is most often reflective of decreased tubular secretion and not an actual decline in glomerular filtration rate. It should also be noted that the risk of serious adverse effects with trimethoprim-sulfamethoxazole is not dissimilar to many other antibiotics.[2]

Severe adverse reactions to other anti-PCP agents in patients who could not tolerate trimethoprim-sulfamethoxazole therapy (eg, case-reportable instances of acute renal and liver failure with atovaquone) are exceedingly uncommon, although exact instances are difficult to quantify given small sample sizes pertaining to this particular scenario. At this juncture, the need for PCP prophylaxis can be carefully weighed against risk of PCP infection using variables that Schmajuk and Yazdany mention, such as relative degree of immunosuppression and burden of PCP in the community. However, in the cases where the need for PCP prophylaxis is straightforward, such as many of those delineated in our article,[1] the risk of infection far outweighs the risks associated with the prophylactic regimen itself. As is evidenced by the Cochrane review,[3] which was conducted precisely to answer this question, no substantial differences were seen in overall adverse events or in events requiring discontinuation when comparing trimethoprim-sulfamethoxazole with no treatment or placebo in a sample size of 470 patients. Given the fact that PCP infection occurred in the control group with an event rate of more than 6% without prophylaxis, the risks of trimethoprim-sulfamethoxazole–associated adverse events were determined not to outweigh the benefits of preventing PCP infection, which carries a mortality rate of approximately 30% in non-HIV infected patients.[6]

In summary, we agree with Schmajuk and Yazdany that PCP prophylaxis and choice of regimen should be chosen on an individualized basis based on factors such as patient age, presence of comorbidities, interacting drugs, and relative degree of immunosuppression. Additionally, as is the case with all chemoprophylactic regimens, clinical status and treatment course should be continually assessed in each patient and adjusted as indicated. As no prophylactic intervention is ideal, all instances of chemoprophylaxis must be weighed against potential harm when considering whether appropriate for an individual patient, bearing in mind the aforementioned mortality rate carried by PCP in the HIV-negative immunocompromised population.

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Mineralocorticoid Receptor Antagonism Treatment for All Patients With ST-Segment Myocardial Infarction?

To the Editor Dahal and colleagues[1] attempt to shed more light on whether mineralocorticoid receptor antagonism (MRA) benefits outcomes in acute myocardial infarction (MI) with left ventricular ejection fraction (LVEF) greater than 40%, but without heart failure, focusing on ST-segment elevation MI (STEMI).[1] The conclusion of this meta-analysis—that MRA confers a mortality benefit in this group—is somewhat controversial given that none of the 10 trials included showed any mortality benefit in such patients; only 1 (ALBATROSS) suggested a mortality benefit in a nonprespecified STEMI subgroup.[2] Moreover, there is significant heterogeneity in MRA prescribed, time to commencing MRA, reperfusion and revascularization strategies, and medical therapy, all known to influence outcome. The benefits of eplerenone therapy begun 3 to 14 days post-MI in the landmark EPHESUS trial were confined to those who began MRA treatment between days 3 and 7.[3] Day 1 eplerenone treatment reduced a composite clinical/biochemical end point measure in patients with STEMI in REMINDER, driven by reductions in natriuretic peptides but without any mortality benefit.[4] The results of the meta-analysis by Dahal and colleagues[1] must therefore be interpreted with considerable caution.

Whether MRA benefits all patients with STEMI regardless of LVEF remains unanswered but merits further investigation. Remodeling is more prevalent in those with reduced LVEF, but the putative antiremodeling effects of MRA post-MI (observed in preclinical studies) have not been consistently observed in the landmark MRA clinical trials. Nonetheless, the acuteness of arterial occlusion in STEMI not only stimulates activation of extracellular matrix turnover but will undoubtedly result in a sudden drop in LVEF and cardiac output, even if LVEF exceeds 40% at baseline. This in turn potentiates renin-angiotensin-aldosterone system activation, and thus may benefit only a select a group of patients treated with prompt MRA. In a previous study of patients with acute MI, LVEF less than 40%, and without heart failure conducted by my research group,[5] we identified a subgroup of patients with first-time anterior STEMI who displayed attenuated remodeling over 24 weeks among those treated with eplerenone compared with placebo; this subgroup had a lower mean LVEF (36%) than the overall mean LVEF of our cohort (49%), and interestingly a higher mean baseline plasma aldosterone concentration (3.68 vs 2.91 nmol/L; $P < .01$).[5]

Perhaps MRA benefits patients with STEMI regardless of baseline LVEF, although it would seem pathophysiologically intuitive that the lower the LVEF, the greater the MRA effect. Robust, prospective, appropriately powered studies examining the effect of MRA on patients with STEMI and baseline LVEF greater than 40% are required to answer this question once and for all. Until then we should adhere to the current evidence base.

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In Reply We thank Dr Weir for his interest in our article.[1] Although none of the individual trials showed statistically significant reduction in mortality except for ALBATROSS study,[2] cumulative evidence supported the role of mineralocorticoid receptor antagonist (MRA) treatment in patients with acute ST-elevation myocardial infarction (STEMI) without heart failure or left ventricular ejection (LVEF) fraction greater than 40%. The findings of our meta-analysis are consistent with a recently published individual patient level analysis of 2 trials that evaluated MRA therapy in such patients.[3] Although individual studies may be inconclusive, or show conflicting results, meta-analysis may help with cumulative analysis of available research in a topic of interest, which has been demonstrated in the past.[4]