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Study Shows More Than 500 Drugs' Prices Were Hiked in the First Quarter of 2019

More than 500 drugs saw price hikes at the beginning of 2019, including price increases of nearly 3% for generics, according to a new report. Researchers at GoodRx found a 2.9% price hike across brand-name and generic drugs in the first quarter of 2019.

Drug pricing is one of the biggest healthcare issues in politics at present, with both state and federal officials laser-focused on the issue. Department of Health and Human Services Secretary Alex Azar has flagged lower drug prices as a key issue for the agency under his watch.

<https://www.fiercehealthcare.com/keyword/goodrx>

JAMA Pediatr 2019 Apr 29

Autism Can Be Reliably Diagnosed at Age 14 to 16 Months

Should screening start earlier to allow for earlier intervention?

The American Academy of Pediatrics recommends screening for autism spectrum disorder (ASD) at the 18- and 24-month well-child visits, along with regular developmental surveillance. Despite recent evidence suggesting that diagnosis can be made before age 2 years, the average age of ASD detection in the U.S. is between 3 and 4 years.

To determine the youngest age at which ASD testing is reliable, researchers from a large expert autism evaluation center repeatedly evaluated 1269 toddlers referred through a community-based early detection program (which screens for ASD at 12-, 18-, and 24-month well-child visits or through community services). Psychologists performed developmental tests at baseline and every 12 months until children were age 3 years. At each visit, toddlers' diagnosis was designated as ASD, ASD features, developmental delay, language delay, other issue, typically developing, or typical sibling of ASD proband.

At age 12 months, diagnostic stability was weakest; only 50% of ASD cases kept that diagnosis at subsequent visits. Diagnostic stability increased to 79% by 14 months and 83% by 16 months and did not differ by child sex. Many toddlers (24%) transitioned from an initial diagnosis of language/developmental delay to ASD; of note, these later-diagnosed children had significantly worse test scores at their initial visit than typically developing children. Only 2% of toddlers "lost" an ASD diagnosis given at an earlier age.

COMMENT; Although pediatric practices do not yet have a validated tool to screen for ASD at 12 months, it's possible that we could see such a development in the near future. For now, these results show how important it is to reassure parents that it's not “too early” to diagnose autism in toddlerhood, which parents sometimes hear from therapists or teachers. In addition, when ASD evaluations or screeners are borderline, it is important to keep reevaluating children — this is supported by this study's findings that almost one quarter of toddlers didn't meet full ASD criteria until closer to ages 3 and 4 years.

CITATION(S): Pierce K et al. Evaluation of the diagnostic stability of the early autism spectrum disorder phenotype in the general population starting at 12 months. *JAMA Pediatr* 2019 Apr 29; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.0624>)

JAMA Intern Med 2019 May 6

The Impact of Prediagnosis 5-ARIs on Men with Prostate Cancer

Use of 5 α -reductase inhibitors was associated with delayed diagnosis and worse mortality.

5 α -reductase inhibitors (5-ARIs) depress serum levels of prostate-specific antigen (PSA) by approximately 50% and are widely used to reduce the incidence of prostate cancer in patients with benign prostatic hyperplasia. However, whether use of 5-ARIs affects prostate cancer diagnosis and mortality in these patients is unclear.

To address this issue, investigators conducted a population-based cohort study that linked data from the Veterans Affairs Informatics and Computing Infrastructure and the National Death Index on 80,875 patients (median age, 66 years) with a prostate cancer diagnosis made between 2001 and 2015. Of these patients, 10.6% were prescribed 5-ARIs (mainly finasteride) at least 1 year prior to a cancer diagnosis.

The median delay from first adjusted elevated PSA level to prostate biopsy was significantly greater for 5-ARIs users than for nonusers, as was the median adjusted PSA level at biopsy. Users of 5-ARIs were also significantly more likely to have Gleason grade 8 or higher, T3 or greater, node-positive, and metastatic disease than nonusers, as well as higher prostate cancer-specific and all-cause mortality.

COMMENT: As the authors note, given that 5-ARIs suppress PSA and that adjusted PSA values were twice as high among 5-ARI users as nonusers, adjustment for 5-ARI-induced PSA suppression likely was not routinely incorporated in this population. Although the PSA impact of 5-ARI is well appreciated in the urologic community, its penetration into the primary-care setting may not be as robust, thus presenting opportunities for education and highlighting the need for improvement in interdisciplinary communication.

CITATION(S): Sarkar RR et al. Association of treatment with 5 α -reductase inhibitors with time to diagnosis and mortality in prostate cancer. *JAMA Intern Med* 2019 May 6; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.0280>)

Neurology 2019 Apr 17

Utility of Anti-CGRP Antibody Erenumab in Patients with Chronic Migraine with Medication Overuse

Erenumab shows promise in a subgroup analysis of patients with chronic migraine and medication overuse in a phase 2 trial.

Chronic migraine (CM) — defined as 15 or more headache days per month — can be difficult to treat. It is often accompanied by medication overuse (MO), which is the excessive use of acute medications. MO is distinct from medication-overuse headache (MOH), a secondary headache disorder that can result from MO. Cessation of the implicated acute treatments, initiation of preventive treatment, or both are debated treatment options for CM with MO. Three antibodies to calcitonin gene-related peptide (anti-CGRP), including erenumab, have been FDA-approved for preventive treatment of migraine. Can a preventive therapy, such as erenumab, show benefit in patients with CM and MO?

Investigators conducted a preplanned subgroup analysis of the double-blind, placebo-controlled phase 2 trial of erenumab (70 or 140 mg) in patients with CM to assess efficacy based on the presence or absence of MO. Of the 667 patients randomized, 41% met criteria for MO. Compared with the non-MO subgroup, the MO subgroup had a higher percentage with prior treatment failure with at least one preventive treatment (75% vs. 63%) and higher mean baseline monthly migraine days (19.0 days vs. 17.3 days).

At month 3, patients in the MO subgroup experienced reduced mean monthly migraine days with erenumab versus placebo (140 mg: -6.6 days; 70 mg: -6.6 days placebo: -3.5 days) and acute migraine-specific medication treatment days (140 mg: -4.9 days; 70 mg: -5.4 days; placebo: -2.1 days). The observed treatment effects were similar in the non-MO subgroup.

COMMENT: This exploratory analysis shows benefit from preventive therapy with erenumab in a subgroup of patients that is often considered difficult to treat. Importantly, the studied population had MO; these results may not generalize to patients with MOH. A recent study of a rat model of MOH suggests a potential role for anti-CGRP antibodies (*Cephalalgia* 2017; 37:560), but clinical research is required.

Dr. Juliana VanderPluym is Assistant Professor of Neurology, Mayo Clinic, Scottsdale, Arizona, and has received a grant from the manufacturer of erenumab for work unrelated to this study.

CITATION(S): Tepper SJ et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. *Neurology* 2019 Apr 17; [e-pub]. (<https://doi.org/10.1212/WNL.0000000000007497>)

Ann Intern Med 2019 May 7

Many Large Clinical Trials Have Gone Missing

In a single survey, results on studies involving almost 90,000 people were never reported, potentially skewing the medical evidence base.

In medicine, we depend on the medical literature. However, what we cannot see — what is missing from the literature — might also be important. In the last decade, many studies have revealed that scientists conducting clinical trials too commonly do not provide the results publicly. Although some experts have suggested that trials with unreported data are mostly inconsequential, others have provided data that cast doubt on that belief.

To explore this issue further, Tatsioni and colleagues started with a search on ClinicalTrials.gov for long-unpublished, large, randomized trials that started after June 1, 2007, and were completed before June 1, 2012; the authors focused on the 500 trials with the largest number of participants. Trials for which the investigators did not publish the study or report results at ClinicalTrials.gov as of April 22, 2016, were then further assessed through January 2019.

The authors identified 67 preregistered but unreported trials, with a median enrollment of 765 (range, 511–11,000), which were unreported for a median of 9 years postcompletion. The total number of participants involved was 87,883; more than half of the trials were conducted in the U.S.

COMMENT: This study demonstrates clearly that unreported large trials occur with an uncomfortable frequency. In sum, investigators of these studies conducted human experiments on almost 90,000 people and failed to inform the world of the results. That we, as a profession and scientific community, allow this to occur is simply unacceptable. The sharing of results is the responsibility of all scientists — and is our ethical obligation to the participants. It is far past time to address this situation and restore trust in clinical science.

Dr. Krumholz had no involvement in this study but did coauthor the accompanying editorial.

CITATION(S): Tatsioni A et al. Lost evidence from registered large long-unpublished randomized controlled trials: A survey. *Ann Intern Med* 2019 May 7; [e-pub]. (<https://doi.org/10.7326/M19-0440>)

Wallach JD and Krumholz HM. Not reporting results of a clinical trial is academic misconduct. *Ann Intern Med* 2019 May 7; [e-pub]. (<https://doi.org/10.7326/M19-1273>)
