

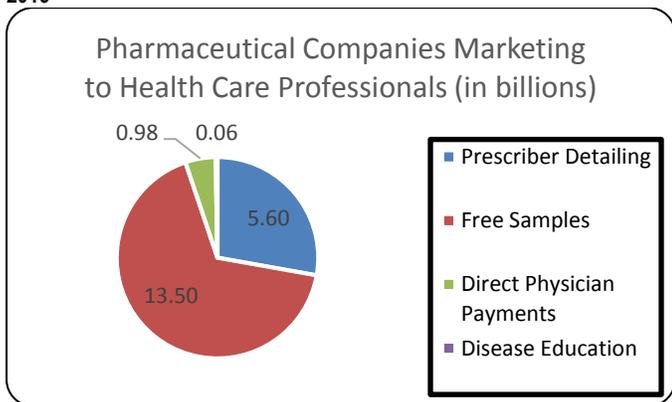
## Evidence for Drugs that are Heavily Marketed

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Direct-to-consumer (DTC) advertising of pharmaceuticals is only allowed in 2 countries worldwide, the United States (U.S.) and New Zealand. Billions of US dollars are spent on DTC advertising on an annual basis. The utility of such marketing has not been associated with improved patient outcomes, but does correlate with increased public interest in promoted drugs.<sup>1</sup> Constructive conversations between providers and their patients are a critical part of making informed evidence-based drug therapy choices. The purpose of this newsletter is to evaluate the evidence for commonly marketed drugs, determine place in therapy, and suggest more cost effective treatment options.

A recent study published in the *Journal of the American Medical Association* (JAMA) found that DTC advertising increased from \$2.1 billion dollars in 1997 to \$9.6 billion dollars in 2016.<sup>2</sup> The primary drivers of the increased advertisement spending were high-cost biologicals and cancer immunotherapies. Marketing to health care professionals also increased from \$15.6 billion to \$20.3 billion within the same 19-year time span (Figure 1).<sup>2</sup> Since 1997, \$11 billion in fines for off-label or deceptive marketing have also been paid out by drug companies.<sup>2</sup> Manufacturers are willing to invest in DTC advertising because of the proven influence on prescribing practices.<sup>1</sup>

**Figure 1. Dollars Spent on Marketing to Health Care Professionals in 2016<sup>2</sup>**



The most actively marketed drugs change from year to year. In 2019, Xeljanz<sup>®</sup>/Xeljanz XR<sup>®</sup>, Ocrevus<sup>®</sup>, Latuda, and Ozempic<sup>®</sup> television commercials were among the most commonly advertised.

### Xeljanz<sup>®</sup>/Xeljanz XR<sup>®</sup> (tofacitinib)

Over \$150 million have been spent annually on TV marketing for tofacitinib, a Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and moderate-to-severe ulcerative colitis (UC).<sup>3</sup> Advertising for tofacitinib promotes decreased swelling, pain, and joint damage in patients with RA.<sup>4</sup> However, studies of tofacitinib were not able to conclusively show a benefit in progression of structural damage.<sup>5</sup> At 3 months, 31% of patients treated with tofacitinib therapy had symptom reduction compared to 12% of patients on placebo, based on the American College of Rheumatology ACR50 endpoint. ACR50 criteria require at least a 50% reduction in tender and swollen joints and 50% improvement in at least 3 other patient or physician assessments. The ACR50 was 29% for patients with RA who were on methotrexate and tofacitinib versus 8% for patients on methotrexate and placebo.<sup>6</sup> Conventional disease-modifying anti-rheumatic drugs like methotrexate, leflunomide, or sulfasalazine are recommended prior to biologic therapy for RA.<sup>7</sup>

The use of tofacitinib in moderate-to-severe UC is indicated after treatment failure with corticosteroids or tumor necrosis factor (TNF) blockers.<sup>8</sup> No trials have compared tofacitinib to another active treatment in patients with UC to elucidate place in therapy. The absolute difference between tofacitinib and placebo in the number of patients with UC who obtained remission at 52 weeks has ranged from 23-30%.<sup>6</sup> Conventional immunosuppressants (e.g., mercaptopurine, azathioprine, or budesonide) are recommended first for treatment of UC before treatment with a biologic agent.<sup>8</sup>

Tofacitinib carries a Food and Drug Administration (FDA) boxed warning for risk of serious infection, mortality, malignancy and thrombosis, so it especially important to carefully consider the risks versus benefits of therapy.<sup>8</sup>

- Oregon Health Plan (OHP) Fee-For-Service (FFS) policy requires a prior authorization approval for all biologics used for autoimmune diseases
- A trial of conventional treatments are required before approval of biologic therapy
- The cost of first-line treatments, such as methotrexate, are \$7 compared to \$4300 for tofacitinib, based on the 30-day average actual acquisition cost (AAAC)\*

\* Myers and Stauffer. Oregon Health Authority Average Actual Acquisition Cost (AAAC) Rate Listing for Generic Drugs. December 21, 2019.

### Ocrevus<sup>®</sup> (ocrelizumab)

Ocrelizumab is approved for treatment of multiple types of multiple sclerosis (MS) in adults, including clinically isolated syndrome, relapsing-remitting disease (RRMS), active secondary progressive disease, and primary progressive multiple sclerosis (PPMS).<sup>9</sup> In November 2019, the total spending on TV advertisements for ocrelizumab was \$17.6 million.<sup>3</sup> The advertisements promoted reduction in relapses for patients with RRMS, as well as slowing disability of progression in PPMS and relapsing MS (RMS).<sup>10</sup> Most patients with RRMS in these studies only had mild disability. An evidence summary from these ocrelizumab trials are as follows:

- Evidence for ocrelizumab in patients with PPMS is of low quality. Disease progression over 12 weeks (as assessed by the Expanded Disability Score [EDSS]) occurred in 32.9% of patients treated with ocrelizumab and 39.3% of patients on placebo (absolute risk reduction [ARR] 6.4% and number-needed-to-treat [NNT] 16).<sup>11</sup>
- More patients with PPMS treated with ocrelizumab dropped out of trials early versus patients on placebo, potentially falsely increasing the percentage of patients with disability progression, which could have biased the results in favor of ocrelizumab.
- The efficacy of ocrelizumab appears to wane after 18 weeks in patients with PPMS.<sup>11</sup>
- When ocrelizumab was compared to interferon beta-1a in patients with RRMS over 96 weeks, the annualized relapse rates (average number of relapses a group of patients in the study had in one year) were 0.16 and 0.29, respectively, in studies that provided moderate quality evidence.<sup>11</sup>

Ocrelizumab is associated with a higher rate of infusion-related reactions compared to beta-1a in patients with RRMS (34% vs. 10%).<sup>9</sup>

- Interferons are recommended first-line for the management of MS and are the most cost-effective option
- Ocrelizumab is available for OHA FFS patients if clinical prior authorization criteria are met

### Latuda (lurasidone)

Lurasidone is indicated for treatment of schizophrenia and bipolar depression (bipolar I disorder) in adults and pediatric patients, as monotherapy or as adjunctive therapy with lithium or valproate.<sup>12</sup> TV advertisements for lurasidone use in bipolar depression exceeded \$26 million in a 2-month period of October and November 2019.<sup>3</sup> Commercials offered vague statements about the drug's efficacy, such as "efficacy is proven for many people with bipolar depression" and that "it is the number one prescribed therapy for bipolar depression."<sup>13</sup> Patients with bipolar depression treated with lurasidone reported 4.7-point improvement in the Montgomery-Asberg Depression Rating Scale [MADRS] versus patients on placebo (-15.4 points vs. -10.7 points, respectively).<sup>12</sup> When lurasidone was studied as adjunctive therapy with lithium or valproate, patients on lurasidone improved by 3.6 points more on the MADRS than patients on placebo with lithium or valproate.<sup>12</sup> The observed improvements in MADRS scores were significant but none of the studies demonstrated remission of depression, as indicated by a MADRS score of less than or equal to 12.<sup>14</sup> No evidence of efficacy was found for doses greater than 60 mg per day. Lurasidone has a FDA boxed warning for the risk of increased mortality in elderly patients and increased risk of suicidal thoughts.<sup>12</sup>

- For acute bipolar depression, first-line therapies recommended by the Mental Health Clinical Advisory Group (MHCAG) include lamotrigine, lithium, and quetiapine
- Lurasidone is only recommended as 2<sup>nd</sup>-line therapy for acute bipolar depression
- MHCAG treatment algorithms for schizophrenia and bipolar disorder are available at: <https://www.oregon.gov/oha/HSD/OHP/Pages/PT-MHCAG.aspx>
- The cost of lurasidone is more than 20-times higher than olanzapine, which is also approved for bipolar I disorder

### Ozempic® (semaglutide)

Semaglutide is a once-weekly glucagon-like peptide receptor agonist (GLP-1 RA) indicated for adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.<sup>15</sup> TV advertisement expenditures for semaglutide are about \$15 million per month.<sup>3</sup> Commercials emphasize glucose lowering and cardiovascular (CV) risk. Hemoglobin A1c (HbA1c) reductions observed with semaglutide are similar to other GLP-1 RAs, ranging from -0.27% to -1.56%.<sup>16</sup> However, patient outcomes beyond 2 years is unknown. The FDA requires all diabetes therapies undergo CV risk assessment. Some T2DM treatments have shown to reduce CV risk in patients, but no increase or decrease in CV risk has been demonstrated with semaglutide.<sup>15</sup> Adverse events associated with semaglutide, most commonly gastrointestinal effects, are similar to other GLP-1 RAs.<sup>15</sup>

- OHA FFS policy recommends semaglutide after trial or contraindication to metformin and sulfonylurea
- Semaglutide is not on the OHP FFS preferred drug list
- Semaglutide is about 30% more expensive than the weekly formulation of exenatide, which is a preferred drug on the OHP FFS preferred drug list\*

\* Myers and Stauffer. Oregon Health Authority Average Actual Acquisition Cost (AAAC) Rate Listing for Generic Drugs. 21 December 2019.

### Conclusion

The DTC advertising concept has captured market share and influenced prescribers and patients for years. Newer, heavily marketed therapies have been shown to be effective in short-term studies, but often lack evidence to show improved patient outcomes over similar, yet more established therapies. With health care costs in the U.S. unlike any developed nation, it is important that evidenced-based therapies that have demonstrated efficacy and safety over time are used first before new drugs with insufficient evidence of clinical superiority are prescribed.

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