Cross-sectional study of medical advertisements in a national general medical journal: evidence, cost, and safe use of advertised versus comparative drugs

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Abstract

Background: Healthcare professionals are exposed to advertisements for prescription drugs in medical journals. Such advertisements may increase prescriptions of new drugs at the expense of older treatments even when they have no added benefits, are more harmful, and are more expensive. The publication of medical advertisements therefore raises ethical questions related to editorial integrity.

Methods: We conducted a descriptive cross-sectional study of all medical advertisements published in the Journal of the Danish Medical Association in 2015. Drugs advertised 6 times or more were compared with older comparators: (1) comparative evidence of added benefit; (2) Defined Daily Dose cost; (3) regulatory safety announcements; and (4) completed and ongoing post-marketing studies 3 years after advertising.

Results: We found 158 medical advertisements for 35 prescription drugs published in 24 issues during 2015, with a median of 7 advertisements per issue (range 0 to 11). Four drug groups and 5 single drugs were advertised 6 times or more, for a total of 10 indications, and we made 14 comparisons with older treatments. We found: (1) ‘no added benefit’ in 4 (29%) of 14 comparisons, ‘uncertain benefits’ in 7 (50%), and ‘no evidence’ in 3 (21%) comparisons. In no comparison did we find evidence of ‘substantial added benefit’ for the new drug; (2) advertised drugs were 2 to 196 times (median 6) more expensive per Defined Daily Dose; (3) 11 safety announcements for five advertised drugs were issued compared to one announcement for one comparator drug; (4) 20 post-marketing studies (7 completed, 13 ongoing) were requested for the advertised drugs versus 10 studies (4 completed, 6 ongoing) for the comparator drugs, and 7 studies (2 completed, 5 ongoing) assessed both an advertised and a comparator drug at 3 year follow-up.

Conclusions and relevance: In this cross-sectional study of medical advertisements published in the Journal of the Danish Medical Association during 2015, the most advertised drugs did not have documented substantial added benefits over older treatments, whereas they were substantially more expensive. From January 2021, the Journal of the Danish Medical Association no longer publishes medical advertisements.
Introduction
The pharmaceutical industry promotes prescription drugs in many ways, e.g. through sales visits to medical personnel, by arranging conferences with key opinion leaders, distributing reprints of studies published in prestigious medical journals, and through print advertisements [1]. Medical advertisements directed towards patients, often called “direct to consumer” advertisements, are allowed only in a few countries, including the United States and New Zealand. Opponents argue that these advertisements medicalise normal experiences and lead to unnecessary drug use [2]. Advocates argue that such advertisements increase patients’ autonomy and raise awareness about new treatments and diseases that would otherwise remain underdiagnosed and undertreated [3].

To our knowledge, medical advertisements for health care professionals, i.e. marketing content about new prescription drugs sponsored by pharmaceutical companies, are allowed in most countries and published in most medical journals. Researchers have recommended medical journals to abandon such advertisements arguing that they make medical doctors prescribe new drugs at the expense of older, cheaper, and often equivalent or better alternatives [4]. PLOS Medicine is likely one of the few medical journals that has chosen to not bring medical advertisements. At the journal’s inauguration, the editors stated they did not want to be part of a “cycle of dependency” with the pharmaceutical industry [5]. The International Committee of Medical Journal Editors (ICMJE) [6] and the World Association of Medical Editors (WAME) [7] recommend against medical advertisements to be juxtaposed to related scientific content. A case-control study of four international and three Russian medical journals (total of 214 issues) found 90 instances of advertisements published in an issue with closely related scientific content [8].

Medical advertisements may refer to data that do not substantiate claims or to data that is inaccessible [9–14], and they may present relative rather than absolute treatment effects, which could lead to exaggerated perceptions of treatment effects [15]. One third of antidepressant advertisements published in the Journal of the Swedish Medical Association between 1994 to 2003 violated the industry’s own code of conduct [16], and 82% of medical advertisements published in a sample of American medical journals in 2008 did not comply fully with the US Food and Drug Administration (FDA) advertising guideline [17]. A systematic review of the quality of medical advertisements reported that only 8% of the advertisements’ statements cited systematic reviews and 30% randomised trials [18]. Another systematic review found that exposure to pharmaceutical promotion was associated with increased prescription rates and costs, and lower quality of prescriptions, whereas there was no evidence of improved prescription quality, defined, for example, as adherence to prescription guidelines and appropriateness of prescriptions [19].

In this study we wanted to investigate which drugs were advertised in the Journal of the Danish Medical Association [20]. Additionally, for the most commonly advertised drugs, we wanted to assess the evidence for added benefit, cost, safety announcements, and drug regulator required post-marketing studies comparing with older prescription drugs for the same indication.

Methods
We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [21] for reporting our results.

The medical journal
The Journal of the Danish Medical Association [20] is a general medical journal and a member of the International Committee of Medical Journal Editors (ICMJE). The journal is published biweekly in Danish and circulated in print to all members of the Danish Medical Association, which has approximately 30,000 medical doctors as members.

Sample of advertisements
Two observers (KB and ALS) independently assessed all issues of the Journal of the Danish Medical Association published in 2015 (excluding special issues). A third author (KJ) arbitrated in case of disagreements. We extracted information from all medical advertisements published during 2015. We did not include advertisements for over-the-counter drugs, dietary supplements, or medical devices. We extracted the following information: trade name, generic name, drug class, indication, and sponsor. We categorised each advertisement according to the most relevant medical specialty. We looked up each advertisement’s indication (e.g. hypercholesterolaemia) in a Danish medical reference [22] and adopted its specialty categorisation (e.g. endocrinology).

In the European Union, medical advertisements must be juxtaposed by the product information, the Summary of Product Characteristics (SmPC) [23]. Some SmPCs may resemble actual advertisements by including logos, illustrations, tables, or descriptive text in addition to the mandated text. We therefore included those SmPCs that contained more than the legally required [23] information as advertisements. The results were summarised in Excel and are presented as summary statistics, i.e. percentages and medians.

Advertisements coinciding with scientific content
We assessed whether advertisements for speciality drugs, i.e. drugs that are used and prescribed by specialists,
appeared in issues with related scientific articles, e.g. narrative reviews related to the specialist drug.

Comparison of most commonly advertised drugs versus older comparators
One author (KB) assessed the most advertised drugs with 6 or more advertisements. We grouped advertised drugs if they belonged to the same drug class, e.g. combination beta₂-agonist and steroid formulations, or if they were advertised for the same specific indication, e.g. treatment of atrial fibrillation. We compared these most commonly advertised drugs or drug groups, with clinically relevant comparators. We defined the relevant comparators as single components of combination formulations, regular pill formulations of modified release formulations, or first-choice treatments for the advertised condition. See also the Supplementary file, eMethods. We made four analyses for these advertised drugs and their relevant comparators:

1. Evidence for added benefits

We searched for direct comparative evidence in Cochrane reviews, the Institute for Quality and Efficiency in Healthcare’s (IQWiG) assessment reports, FDA Medical Office Reviews and the European Medicines Agency’s (EMA) Public Assessment Reports, in that order. We categorised the evidence for added benefit of the advertised drug (for the advertised indication) relative to the comparator as ‘substantial added benefits’, ‘uncertain benefits’, ‘no added benefits’, or ‘no evidence’. See also Supplementary file, eMethods for details.

2. Defined Daily Dose cost analysis

We compared the advertised drugs’ Defined Daily Dose to those of the relevant comparators. We obtained prices from the Danish Medicines Agency [24].

3. EMA and FDA safety announcements

We searched the FDA Drug Safety Communication [25] archive and EMA’s medicines database [26] for safety announcements pertaining to the advertised drugs and their relevant comparators. We searched for announcements published within a three-year follow-up period after advertising between 2015 and 2018.

4. Post-marketing studies

We searched for drug regulator required post-marketing studies registered in the FDA Postmarket Requirements and Commitments database [27] and the European Union electronic Register of Post-Authorisation Studies [28]. We categorised the studies according to their status at 3 years of follow-up (December 2018) from advertising as: ‘completed’ (results reported before December 2018), or ‘ongoing’ (results reported, or planned to be reported, after December 2018). See the Supplementary file, eMethods for details.

Results
Summary results
During 2015, there were 158 medical advertisements for 35 different prescription drugs, published in 24 issues with a median of 7 per issue (range 0 to 11). Of the 158 advertisements, 35 (22%) were Summary of Product Characteristics that contained more than the legally required text. In two issues (no. 19 and no. 23), seven of the first nine pages were medical advertisements or SmPCs. In the two issues published during Danish summer holiday (July), there were no advertisements. See the full list of advertisements in Supplementary file, eTable 1. Drugs often prescribed in general practice were the most frequently advertised. Advertisements for pulmonology appeared most frequently (n = 57, 36%), followed by psychiatry (n = 32, 20%), analgesics (n = 17, 11%), endocrinology (n = 15, 8%), and urology (n = 8, 5%), see Supplementary file, eTable 2.

Advertisements coinciding with scientific content
We found seven cases of advertisements for six specialist drugs appearing in issues with related scientific content, Supplementary file eTable 3. In three cases, the advertised drugs were directly mentioned in narrative reviews appearing in the same issue. In four cases, the advertisements appeared in issues with closely related scientific content, but the drugs were not directly mentioned.

Comparison of most commonly advertised drugs versus older comparators
Four drug groups, combined beta₂-agonist + steroid inhalations (three drugs), combined beta₂-agonist + anticholinergic agent inhalations (three drugs), ADHD medications (two drugs), and new oral anticoagulants (two drugs) and five single drugs, modified-released paracetamol, vortioxetine, aripiprazole intramuscular depot, pneumococcal vaccine, and canagliflozin, were advertised ≥6 times during 2015, Table 1. The sample accounted for 118 (75%) of the 158 advertisements. We compared these frequently advertised drugs with older comparators in four analyses:

1. Evidence for added benefits

The most advertised drugs (four drug groups, five single drugs) were advertised for 10 different indications and we made 14 comparisons with older comparators,
Table 2. We used Cochrane systematic reviews (six comparisons), IQWiG reports (two), FDA reports (two), EMA report (one), and a single trial for one comparison. For two comparisons we found no evidence source. We included additional evidence outside of our stipulated search strategy for four comparisons (beta 2-agonist + steroid combination for asthma, atomoxetine for adult ADHD, vortioxetine for depression, and pneumococcal vaccines for invasive pneumonia), Table 2.

The advertised drugs had evidence of ‘substantial added benefits’ compared to older relevant comparators in none (0%) of the comparisons, there were ‘uncertain benefits’ in seven (50%) comparisons, and evidence of ‘no added benefits’ of the advertised drugs in four (29%) comparisons. For three (21%) comparisons there was ‘no evidence’, Table 2. See the Supplementary file, ‘Evidence for the advertised drugs’ and eTable 4, for details on each comparison.

2. Defined Daily Dose cost analysis

The advertised drugs were two to 196 times (median of 6) more expensive measured as the Defined Daily Dose than the older comparators, Table 3. For unknown reasons, the Danish Medicines Agency did not report the Defined Daily Dose for inhalation combination drugs, and we could not make a price comparison for the pneumococcal vaccine against placebo.

3. EMA and FDA announcements

Between 2015 and 2018, EMA and FDA made 11 announcements related to five of the advertised drugs, and one announcement also pertained to a relevant comparator (FDA’s warning on aripiprazole), Table 4. The FDA issued nine Drug Safety Communications (canagliflozin = 7; aripiprazole = 1; combined beta 2-agonist and steroid inhalation formulation = 1) and EMA issued two Referrals (inhaled corticosteroids for chronic obstructive pulmonary disorder (COPD) and modified-release paracetamol). Most warnings related to new harms, whereas one safety announcement informed that combination beta 2-agonist + steroid inhalation formulation was not increased the risk of serious asthma related outcomes. EMA’s Referral on modified-release paracetamol announced the drug’s withdrawal from the European market due to difficulties in managing drug overdoses.
4. **Post-marketing studies**

We identified 37 drug regulator requested post-marketing studies, 33 in the EU database and four in the FDA database. By December 2018, 12 studies were completed and 25 were ongoing, Table 5. Twenty (54%) post-marketing studies (7 completed, 13 ongoing) related to the advertised drugs (beta2-agonist + anticholinergic combinations = 4; canagliflozin = 5; combined beta2-agonist + steroid = 3; rivaroxaban = 3; vortioxetine = 2; aripiprazole, dabigatran, and lisdexamfetamine one each), Supplementary file eTable 5. Ten (27%) studies (4 completed, 6 ongoing) related to four comparator drugs (duloxetine = 5; methylphenidate = 2; umecclidinium = 2, metformin = 1), Supplementary file eTable 7.

The postmarketing studies assessed specific harms (24, 65%), benefits and harms (11, 22%), and prescription patterns (2, 5%), e.g. off-label use. All studies had an observational design, e.g. pharmacovigilance and cohort studies, except one randomised clinical trial for the antidepressant vortioxetine.

### Discussion

#### Key results

To our knowledge, this is the first cross-sectional study to assess all medical advertisements published in a general medical journal throughout a calendar year. We judged that none of the most frequently advertised drugs were supported by evidence of ‘substantial added benefits’ compared to relevant comparators. This

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**Table 2** Comparative evidence for the most advertised drugs and drug groups

| Advertised drug                  | Indication                        | Comparison                                    | Reviewed evidence                        | Evidence categorisation |
|----------------------------------|-----------------------------------|-----------------------------------------------|------------------------------------------|-------------------------|
| **Drug groups**                  |                                   |                                               |                                          |                         |
| 1. Beta2-agonist + steroid       | 1. Asthma                          | 1. Steroid inhalation only                    | Systematic review [29] + FDA analysis [30] | Uncertain benefits     |
| inhalations                      | 2. COPD                            | 2. Beta2-agonist inhalation only              | Systematic review [31]                  | Uncertain benefits     |
| -                                 |                                   |                                               |                                          |                         |
| 2. Beta2-agonist + anti-         | 2. COPD                            | 3. Beta2-agonist only                        | Systematic review [32]                  | Uncertain benefits     |
| cholinergergic agents            |                                   | 4. Anticholinergic agent only                 | Systematic review [32]                  | Uncertain benefits     |
| -                                 |                                   |                                               |                                          |                         |
| 3. ADHD medications              |                                   |                                               |                                          |                         |
| Lisdexamfetamine                 | 3. ADHD                            | 5. Methylphenidate                            | No evidence source                      | No evidence             |
| Atomoxetine                      | 3. ADHD                            | 6. Methylphenidate                            | One clinical trial [33]                 | No added benefits      |
| **New oral anticoagulations**    |                                   |                                               |                                          |                         |
| Rivaroxaban                      | 4. Atrial fibrillation             | 7. Warfarin                                   | FDA report [34]                         | No added benefits      |
| Dabigatran                       | 4. Atrial fibrillation             | 8. Warfarin                                   | FDA report [35]                         | No added benefits      |
| **Single drugs**                 |                                   |                                               |                                          |                         |
| 5. Paracetamol modified-release  | 5. Pain                            | 9. Regular paracetamol                         | No evidence source                      | No evidence             |
| 6. Vortioxetine                   | 6. Depression                      | 10. Duloxetine                                | Systematic review [36]                 | No added benefits      |
| 7. Aripiprazole intramuscular     | 7. Schizophrenia                   | 11. Aripiprazole oral tablet                  | EMA report [37]                         | Uncertain benefits     |
| depot                             |                                   |                                               |                                          |                         |
| 8. Pneumococcal vaccine          | 8. Pneumococcal pneumonia         | 12. Placebo                                   | Systematic review [38] + clinical trial [39] | Uncertain benefits     |
| 9. Canagliflozin                 | 9. Diabetes mellitus type 2 (single | 13. Glimeride                                 | IQWiG report [40]                      | No evidence             |
| -                                 | therapy)                          | 14. Glimeripride add-on to metformin          | IQWiG report [40]                      | Uncertain evidence      |

ADHD attention deficit hyperactivity disorder; COPD chronic obstructive pulmonary disorder. *For four comparisons we included evidence identified outside our stipulated search strategy. We have detailed this in the Supplement, eTable 8.
corresponds with recent reports that the evidence for the majority of new cancer drugs and newly authorised drugs in Germany demonstrate little or no added patient-relevant benefits over existing treatments. Our analyses highlight, perhaps unsurprisingly, that advertised drugs were substantially more expensive than existing drugs on the market, which may be important in the light of the poor evidence for added value to the patients. Finally, we found that there were numerically more safety announcements issued regarding newly identified harms and more uncompleted post-marketing studies addressing potential harms related to the advertised drugs at three years of follow-up. This may indicate a larger uncertainty related to the clinical use of newer drugs compared to older comparators. In general, our study seems to add to the existing literature that medical advertisements directed towards healthcare professionals may not have beneficial effects but may have important negative effects.

**Interpretation**

We published an abridged version of this paper as an opinion piece in the *Journal of the Danish Medical Association* in 2018 in Danish and encouraged the Danish Medical Association to ban medical advertisements.

### Table 4 EMA and FDA safety announcements published after advertising (2015–2018)

| Drug                                      | Clinical findings                                                                 | Regulator | Regulatory action                                      | Announcement  |
|-------------------------------------------|-----------------------------------------------------------------------------------|-----------|--------------------------------------------------------|--------------|
| Canagliflozin                             | Increased risk of ketoacidosis                                                    | FDA       | Undertaking further investigations (all SGLT2-inhibitors) | May 2015 [41] |
| Canagliflozin                             | Increased risk of bone fractures and decreased bone mineral density               | FDA       | Warning added to the FDA prescriber information         | Sep 2015 [42] |
| Canagliflozin                             | Increased risk of ketoacidosis, urosepsis, and pyelonephritis                     | FDAa      | Warning added to the FDA prescriber information (all SGLT2-inhibitors) | Dec 2015 [43] |
| Aripiprazole                              | Impulse-control problems (gambling, binge eat, shop, sex)                         | FDA       | Warning added to the FDA prescriber informationa        | May 2016 [44] |
| Canagliflozin                             | Interim results: Increased risk of leg and foot amputations                       | FDA       | Undertaking further investigations                      | May 2016 [45] |
| Canagliflozin                             | Risk of acute kidney injury                                                       | FDA       | Revised warning on the FDA prescriber information       | June 2016 [46] |
| Inhaled corticosteroids for COPD          | Increased risk of pneumonia                                                       | EMA       | Updated product information                              | July 2016 [47] |
| Canagliflozin                             | Increased risk of foot and leg amputation                                          | FDAa      | Addition of FDA boxed warning                           | May 2017 [48] |
| Combined beta2-agonist + steroid inhalation| No increased risk of serious asthma-related outcomes                              | FDA       | Removal of FDA boxed warning                            | Dec 2017 [49] |
| Modified-release paracetamol              | Difficulties in managing overdoses                                               | EMA       | Withdrawal of product from EU market                    | Dec 2017 [50] |
| Canagliflozin                             | Increased risk of necrotising fasciitis of the perineum                           | FDA       | Warning added to the FDA prescriber information (all SGLT2-inhibitors) | Aug 2018 [51] |

Announcements listed in chronological order. *The warning pertained to all formulations of aripiprazole, both oral tablet and intramuscular injections. *Similar referral issued by EMA.
On 19 June 2020, the Delegation of the Danish Medical Association voted to abolish medical advertisements [55] and, to our knowledge, this may be the first national medical association to make such a decision. We do not know if, and if so, to what degree, our work [54, 56] and advocacy for banning medical advertisements influenced this decision.

Nevertheless, an important question remains whether other medical associations, medical societies, and their respective medical journals could and should follow suit and abolish such advertisements. We are not aware of discussions regarding such a ban of advertisements for healthcare professionals in Europe. In contrast, on several occasions the introduction of ‘direct to consumer’ advertisements have been proposed to the European Commission [57, 58]. Similarly, we are not aware of discussions in the United States related to a ban of these advertisements directed at healthcare professionals, despite pharmaceutical companies spending more money on marketing directed at healthcare professionals than on ‘direct to consumer’ marketing. In 2016, a total of $20.3 billion was spent on marketing directed at healthcare professionals in the US compared to $9.6 billion on “direct to consumer” marketing [59]. Interestingly, it has long been debated in the US whether ‘direct to consumer’ advertisements should be banned [60] and in 2015, the American Medical Association advocated for such a ban stating these advertisements increase the use

Table 5 Post-marketing studies ongoing at three year follow-up after advertising (Dec 2018)

| Drug                                   | Study ID                          | Requested | Clinical question                                      |
|----------------------------------------|-----------------------------------|-----------|-------------------------------------------------------|
| **Advertised drugs**                   |                                   |           |                                                       |
| Aripiprazole IM                        | EUPAS21056                        | EMA       | Specific harms (extrapyramidal symptoms)              |
| Canagliflozin                          | EUPAS27670                        | EMA       | Specific harm (lower limb amputations)                |
| Canagliflozin (NDA 204042 commitment no. 1) | FDA   | Specific harm (ketoacidosis)                      |
| Canagliflozin (NDA 204042 commitment no. 3) | FDA   | Specific harm (various conditions)                |
| Fluticasone propionate / formoterol    | EUPAS3702a                        | MHRA      | Benefits and harms                                    |
| Lisdexamfetamin                        | EUPAS20546                        | EMA       | Specific harm (cardiovascular events)                 |
| Rivaroxaban                            | EUPAS11299, EUPAS09895, EUPAS11141, and EUPAS11145 | EMA | Specific harms (bleeding events and liver disease)  |
| Tiotropium / olopatad                    | EUPAS14273                        | Japan     | Long-term benefits and harms                          |
| Tiotropium / olopatad                    | EUPAS21574                        | EMA       | Specific harms (cardiovascular)                       |
| Tiotropium / olopatad                    | EUPAS14956                        | South Korea | Benefits and harms                                    |
| Umeclidinium/vilanterol                 | EUPAS9868                         | Japan     | Benefits and harms                                    |
| Umeclidinium/vilanterol                 | EUPAS11397                        | South Korea | Benefits and harms                                    |
| Vortioxetine                           | NDA 204447 commitment no. 6       | FDA       | Benefits and harms                                    |
| Vortioxetine                            | EUPAS19199                        | EMA       | Clinical use and several specific harms               |
| **Comparator drugs**                   |                                   |           |                                                       |
| Duloxetine                              | EUPAS20253b                       | United States | Specific harms (maternal and fetal harms)         |
| Duloxetine (NDA 21427 commitment no. 2) | FDA   | Specific harms (maternal and fetal harms)          |
| Methylphenidate                         | EUPAS4551c                        | EMA       | Harms                                                |
| Methylphenidate                         | EUPAS3985c                        | EMA       | Long-term harms                                       |
| Umeclidinium                           | EUPAS14947                        | South Korea | Benefits and harms                                    |
| Umeclidinium                            | EUPAS10224                        | Japan     | Benefits and harms                                    |
| **Advertised drugs and comparator drugs** |                                   |           |                                                       |
| Aclidinium and aclidinium/ formoterol   | EUPAS6559                         | EMA       | Clinical use                                          |
| Aclidinium and aclidinium/ formoterol   | EUPAS13616                        | EMA       | Specific harms (cardiovascular and mortality)         |
| Dabigatran and rivaroxaban, versus warfarin | EUPAS13017 | France | Benefits and harms                                    |
| Olopatad and olopatad/tiotropin        | EUPAS21574                        | EMA       | Specific harms (cardiovascular events)                |
| Umeclidinium and umelidinium/vilanterol | EUPAS10316 | EMA | Specific harms (cardiovascular and cerebrovascular events) |

**EMA** European Medicines Agency; **FDA** US Food and Drug Administration; **IM** Intramuscular. *The study was scheduled to report data in 2015, but data had not been submitted.* *This study may likely be the same.* *The two methylphenidate studies were planned to finish in 2014 and 2015, but they were listed as ongoing since data had not been reported on the website.*
of more expensive and less effective treatments [61]. The same case could likely be made for advertisements directed at healthcare professionals.

Revenue from medical advertisements is intrinsic to the current biomedical publishing model, along with other revenues, such as sales of re-prints [62]. A cross-sectional study of six medical societies in 1996 estimated that advertising revenue accounted for 2 to 31% of the associations’ total revenue [63]. Major medical publishers report very large profit margins, e.g. Informa (who owns Taylor & Francis) reported an operating profit of £933 million (32%) of a total revenue of £2.9 billion in 2019 (p. 161) [64]. Elsevier reported an adjusted operating profit of £982 million (37%) of a total revenue of £2.6 billion in 2019 [65]. Interestingly, only 2% of this revenue came from advertising whereas subscription fees was the major source of income (p. 16) [65]. An informed guess is therefore that abolishing of medical advertisements is economically feasible for major journals and publishers.

The impact on public health of advertisement to healthcare professionals may also not be trivial. The current ‘opioid crisis’ has been associated with marketing of OxyContin directed towards doctors falsely highlighting its low potential for addiction [66]. An American observational study [67] reported a positive association between opioid marketing directed at doctors, prescription rates, and overdose mortality, and registry studies [68, 69] have suggested that a major cause for the recent decrease in the US overall life expectancy is opioid-related mortality. The American Centers for Disease Control and Prevention estimates that nearly 500,000 Americans died because of an opioid related overdose between 1999 and 2019 [70].

Limitations
Our study has several limitations, most importantly the lack of preregistration and specification of our methodology, including pre-defining how to select the comparator drugs. We only assessed advertisements during one year and in one medical journal, yielding a relatively small sample of issues and advertisements, which prevented us from making inferential statistics.

We grouped drugs if they belonged to the same drug class, and some comparisons might therefore have been affected. However, regardless of our preferred ‘unit of analysis’, drugs lumped into groups or individual assessments, our conclusions would likely be similar. For example, the most advertised drug, the combination drug tiotropium/olodaterol indicated for COPD, was included in the ‘beta2-agonist and anti-cholinergic combination’ group. According to an IQWiG report [71], this drug has “proof of lesser benefit” compared to a beta2-agonist or an anti-cholinergic agent alone. Individual drug assessments might even have led to more critical assessments.

While evidence categorisation always contains a degree of subjectivity, we believe that our methods and analyses are transparently reported and that other researchers would likely come to the same conclusions. Some might consider our inclusion of additional evidence outside our stipulated search strategy for some comparisons as unsystematic and potentially biased. It is important to note that the inclusion of this additional evidence did not change our evidence classifications. On the contrary, these efforts illustrate how difficult it may be to obtain the best and most complete available evidence. In fact, difficulties in identifying relevant direct comparisons might illustrate a general problem in the current regulatory drug approval system [53], rather than being a limitation to our project. We consider it an advantage that our evidence categorisation was based on systematic reviews and regulatory drug reports, which often include raw data from pivotal trials.

There might be other approaches to assessing the comparative safety of new versus older drugs than using safety announcements and post-marketing studies as the metric. The number of post-marketing studies does not necessarily indicate a greater uncertainty related to the use of new drugs compared to the older comparators, but rather that new drugs are subject to more scrutiny upon, and after, authorisation. Nevertheless, the higher number of unfinished post-marketing studies and safety announcements imply an uncertainty related to the prescription of these new drugs that did not apply to older comparators. Importantly, these uncertainties may not be conveyed to patients until many years after these drugs have been advertised heavily. Finally, we searched for post-marketing studies related to the single components of the combination inhalation formulations, but we did not search for all authorised single component beta2-agonists, anticholinergic agents, and steroid drugs. However, it is unlikely this would have impacted our overall results.

Generalisability
We assessed a single medical journal during one calendar year and the results may therefore not be generalisable. However, the Journal of the Danish Medical Association is a national general medical journal circulated to all members of the Danish Medical Association across specialties and settings, which makes us believe that the assessed sample of advertised drugs was broad and may reflect well on content in other general medical journals. Our Defined Daily Dose cost analysis applies to Denmark and only at the time of analysis. Cost difference-ratios will be different in other countries and fluctuate over time [72].
We did not assess all advertised drugs, which were beyond the resources available for this research project. The assessed cohort of advertised drugs included commonly used drugs and we believe that our findings likely are transferable to other general medical journals.

Conclusion
In this cross-sectional study of medical advertisements published in a Danish general medical journal during 2015, we did not find evidence of substantial added benefits of the most advertised drugs over older comparators. The advertised drugs were substantially more expensive and likely related to more uncertain use measured on the number of EMA and FDA safety announcements and unfinished post-marketing studies at three years follow-up after the advertisement. The Journal of the Danish Medical Association stopped publishing medical advertisements from 2021.

Supplementary Information
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Authors’ contributions
KB had full access to all the data in the study and takes responsibility for the integrity of the data and the analyses. KB is the guarantor of the study.

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