Do dimethyl fumarate and nicotinic acid elicit common, potentially HCA2-mediated adverse reactions? A combined epidemiological-experimental approach

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**Aim:** Dimethyl fumarate and nicotinic acid activate the hydroxy-carboxylic acid receptor 2 (HCA2) and induce flushing. It is not known whether HCA2 mediates other adverse drug reactions (ADRs) to these two substances. This study aims to compare ADRs associated with dimethyl fumarate and nicotinic acid, and to discuss whether they are HCA2-mediated.

**Methods:** We identified spontaneous reports of suspected ADRs to dimethyl fumarate and nicotinic acid in the European Adverse Drug Reaction Database (EudraVigilance). These reports were analysed at different hierarchical levels of the Medical Dictionary for Regulatory Activities (MedDRA). In addition, we screened murine organs for HCA2 expression.

**Results:** Similarities in the ADR profile of dimethyl fumarate and nicotinic acid included “gastrointestinal signs and symptoms” (odds ratio [OR] 0.8 [0.6-1.1]), “hepatobiliary investigations” (OR 1.3 [0.7-2.5]) and “anxiety disorders and symptoms” (OR 0.9 [0.3-2.2]) in High Level Group Terms; “diarrhoea (excluding infective)” (OR 1.2 [0.7-1.8]) and “liver function analyses” (OR 1.3 [0.7-2.6]) in High Level Terms; and “diarrhoea” (OR 1.2 [0.7-2.0]) and “vomiting” (OR 0.9 [0.4-1.7]) in Preferred Terms. In analogy, HCA2 was expressed in the gastrointestinal tract, liver and central nervous system (CNS) of murine organs. A discrepant ADR profile was seen for “lymphopenia” (n = 777) at the preferred term level (only reported for dimethyl fumarate) and “blood glucose increased” (more often reported for nicotinic acid; OR 0.1 [0.0-0.5]).

**Conclusion:** The gastrointestinal ADRs common to both substances may be mediated by HCA2. Other ADRs not common to both substances are compound or indication-specific reactions and likely do not involve HCA2.
INTRODUCTION

In recent years, dimethyl fumarate has increasingly been used in the treatment of multiple sclerosis and psoriasis. Dimethyl fumarate is rapidly converted into its active metabolite monomethyl fumarate, which activates the nuclear factor (erythroid-derived 2)-like 2 (NRF2) transcriptional pathway and upregulates NRF2-dependent antioxidant genes. However, NRF2-independent mechanisms, including activation of the G protein-coupled receptor hydroxy-carboxylic acid receptor 2 (HCA2, GPR109A), are involved in the therapeutic anti-inflammatory effects as well. HCA2 is expressed in various organs, including skin, intestines and brain. The benefit-harm balance of dimethyl fumarate is considered favourable. Most adverse drug reactions (ADRs) are transient and mild or moderate in severity. ADRs that occur most frequently include flushing, gastrointestinal disorders, eg, diarrhoea, as well as skin and subcutaneous tissue disorders, changes in renal and hepatic laboratory parameters, and lymphopenia. In preclinical models, vasodilatation during flushing response was demonstrated to be mediated by activation of HCA2 in cells of the epidermis.

In addition to dimethyl fumarate’s metabolite monomethyl fumarate, the antisympathetic drug nicotinic acid acts agonistically on the HCA2 receptor. HCA2 mediates at least some of the beneficial effect of nicotinic acid. Interestingly, flushing and gastrointestinal symptoms are among the most common ADRs associated with nicotinic acid, as also with dimethyl fumarate. In preclinical models, administration of dimethyl fumarate or nicotinic acid resulted in a bi-phasic flushing response caused by HCA2-expressing cells of the epidermis. HCA2 activation in Langerhans cells and keratinocytes stimulated the release of prostaglandin D2 and E2, leading to vasodilation in the dermis. Apart from flushing, it is not known whether HCA2 mediates other ADRs that develop during treatment with dimethyl fumarate or nicotinic acid.

With the concept in mind that HCA2 may mediate some of the ADRs to dimethyl fumarate and nicotinic acid, we compared the ADR profiles of the two drugs. For this purpose, we combined an epidemiological with an experimental-pharmacological approach. For the epidemiological approach we analysed spontaneous reports of suspected ADRs to these two substances. For the experimental approach, we screened selected mouse organs for expression of HCA2. To explore the role of HCA2 in dimethyl fumarate- and nicotinic acid-induced diarrhoea, we localised HCA2 in the gastrointestinal tract and investigated the intestinal mucosa of mice with an Ussing chamber. In connection with experimental data, the analysis of spontaneous reports of suspected ADRs can provide clues to the mechanisms underlying these effects. Understanding the pathomechanisms of HCA2-mediated ADRs is helpful for developing strategies to improve the safety and tolerability of receptor agonists. The aim of the present study was to compare the ADR profiles of dimethyl fumarate and nicotinic acid, and to discuss a possible involvement of the HCA2 receptor.

METHODS

2.1 Analysis of spontaneous reports of suspected ADRs

2.1.1 European adverse drug reaction database EudraVigilance

Detailed information about the reporting obligations of ADRs and the ADR database EudraVigilance can be found elsewhere. In EudraVigilance ADRs are coded using the terminology of the Medical Dictionary for Regulatory Activities (MedDRA), which includes five hierarchical levels: Lowest Level Terms (LLTs), Preferred Terms (PTs), High Level Terms (HLT), High Level Group Terms (HLGTs) and System Organ Classes (SOCs). The SOCs represent the highest, aggregated level of analysis based on the anatomical area in which the ADR develops.
2.1.2 | Identification and analysis of spontaneous reports of suspected ADRs

We identified all spontaneous reports of suspected ADRs (hereinafter referred to as ADR reports) received until 31/05/2019, originating from one of the EEA member states, in which dimethyl fumarate monosubstance (n = 7864), nicotinic acid monosubstance (n = 267), or one of their combination products (dimethyl fumarate plus ethylhydrogenfumarate calcium/magnesium/zinc, n = 807; nicotinic acid/laropiprant, n = 1163) was reported as the “suspected/interacting” drug (query date: 24/06/2019) (Figure 1).

First, a preparatory analysis of the ADR reports of each of the five subgroups was performed. According to this analysis, patients receiving dimethyl fumarate for the indication multiple sclerosis (MS) were younger and more often female, whereas patients receiving nicotinic acid or nicotinic acid/laropiprant were older, had more comorbidities, especially cardiovascular and related disorders, and were more often taking statins.

However, similar ADRs were reported for the three dimethyl fumarate groups except for ADRs that are probably related to the underlying disease (e.g. MS relapse reported in dimethyl fumarate reports with indication MS). As a consequence, one dimethyl fumarate group consisting of the three dimethyl fumarate subgroups (in the following: “dimethyl fumarate reports” [n = 8656]) was created.

Although the combination product nicotinic acid/laropiprant was developed to reduce specific well-known ADRs such as flushing associated with nicotinic acid monosubstance, similar ADRs were observed for both subgroups. Hence, to increase the sample size for nicotinic acid the two subgroups were also combined (in the following: “nicotinic acid reports” [n = 1425]).

2.1.3 | ADR analysis

More detailed analyses of lower MedDRA levels were restricted to those SOCs that appeared most relevant to our analysis due to either sample size or clinical context. Details can be found in the Supporting Information.

The ADR reports of the selected SOCs were further analysed at the HLGT, HLT and PT level. As ADR reports can include two or more ADRs that belong to different SOCs, multiple assignments of single ADR reports to more than one SOC are possible.

2.1.4 | Statistical analysis

Odds ratios (ORs) with Bonferroni-adjusted 95% confidence intervals (CI) were calculated for each comparative analysis of dimethyl fumarate versus nicotinic acid reports at the three hierarchical levels HLGT, HLT and PT. For OR > 1 and CI not including 1, we concluded that the respective HLGT, HLT or PT was more often found in dimethyl fumarate reports. For OR < 1 and CI not including 1, we concluded that the respective HLGT, HLT or PT was more often found in nicotinic acid reports. For OR = 1 and/or CI including 1, we were not able to conclude that there were systematic differences between dimethyl fumarate and nicotinic acid reports regarding the distributions of the respective HLGT, HLT or PT.

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**FIGURE 1** Flowchart: identification of dimethyl fumarate and nicotinic acid reports

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*15 cases were included in both datasets

* in 29 cases the indication was not reported or did not match to MS or psoriasis

*5 cases were included in both datasets
In the results section we present only (i) the 10 most common HLGTs, HLTs or PTs reported for dimethyl fumarate, (ii) the 10 HLGTs, HLTs and PTs with the lowest OR and upper CI < 1, thus more often found in nicotinic acid reports than in dimethyl fumarate reports, and (iii) the 10 HLGTs, HLTs and PTs with an OR closest to 1 and thus similarly frequently reported for dimethyl fumarate and nicotinic acid. Importantly, this is a comparative analysis and the OR does not provide any information about the absolute frequency of ADRs.

For the analysis of HLGTs, HLTs and PTs more often reported in one of the two groups (dimethyl fumarate or nicotinic acid), different arbitrarily chosen thresholds regarding the absolute numbers of ADR reports had to be exceeded. For HLGTs, a threshold of 1% (dimethyl fumarate reports: >87 reports; nicotinic acid reports: >14 reports), for HLTs a threshold of 0.5% (dimethyl fumarate reports: >43 reports; nicotinic acid reports: >7 reports) and for PTs a threshold of 0.25% (dimethyl fumarate reports: >22 reports; nicotinic acid reports: >4 reports) was set.

Thresholds were introduced to reduce incidental similarities and differences in the ADR profiles of dimethyl fumarate and nicotinic acid caused by low case numbers.

### 2.2 HCA2 receptor expression in mouse organs and Ussing chamber experiments

The expression of HCA2 was investigated in various mouse organs. To investigate the role of HCA2 in dimethyl fumarate- and nicotinic acid-induced diarrhoea, murine intestinal tissue was examined with an Ussing chamber. Details of the experimental procedure can be found in the Supporting Information.

### 2.3 Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in [http://www.guidetopharmacology.org](http://www.guidetopharmacology.org), the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.12

### 3 RESULTS

### 3.1 Characteristics of the ADR reports

More males were included in the nicotinic acid reports than in the dimethyl fumarate reports (56.1% vs 24.8%) (Table 1). The patients in the nicotinic acid reports were older (58.4 vs 42.9 years) and had a history of cardiac disorders more often (29.0% vs 0.9%) than the patients in the dimethyl fumarate reports. Almost all (98.7%) nicotinic acid reports were received between 2004 and 2014, whereas 72.8% of the dimethyl fumarate cases were reported between 2017 and 31/05/2019. More than two-thirds (69.1%) of the nicotinic acid reports and roughly half of the dimethyl fumarate reports (47.8%) were from healthcare professionals. Reports from Germany accounted for more than half of the nicotinic acid reports.

### 3.2 Distribution of reported SOCs

In 23.8% (n = 2063) of the dimethyl fumarate reports, the ADRs belonged to the SOC “gastrointestinal disorders” (Supporting Information Figure S1), followed by the SOC “nervous system disorders” (18.1%, n = 1566) and the SOC “investigations” (15.7%, n = 1362). In contrast, the SOC “skin and subcutaneous tissue disorders” ranked first among the nicotinic acid reports (38.4%, n = 548), followed by the SOC “vascular disorders” (31.5%, n = 449) and the SOC “gastrointestinal disorders” (23.7%, n = 338).

With regard to similarities in the ADR profile of dimethyl fumarate and nicotinic acid, the SOCs “gastrointestinal disorders”, “nervous system disorders” and “investigations” accounted for comparable proportions in the dimethyl fumarate and nicotinic acid

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**TABLE 1** Characteristics of dimethyl fumarate and nicotinic acid reports

| Demographic parameters | Dimethyl fumarate reports (n = 8656) | Nicotinic acid reports (n = 1425) |
|------------------------|-------------------------------------|----------------------------------|
| Mean age (median)      | 42.9 (43)                           | 58.4 (60)                        |
| Female                 | 68.0% (5890)                        | 38.5% (549)                      |
| Male                   | 24.8% (2144)                        | 56.1% (799)                      |
| Unknown                | 7.2% (622)                          | 5.4% (77)                        |
| Patient history        |                                     |                                  |
| Cardiac disorders      | 0.9% (78)                            | 29.1% (414)                      |
| Skin and subcutaneous tissue disorders (excluding HLT psoriatic conditions) | 0.7% (62) | 1.2% (17) |
| Psychiatric disorders | 2.7% (233)                          | 2.5% (35)                        |
| Seriousness criteria   |                                     |                                  |
| Serious                | 33.8% (2925)                        | 23.8% (339)                      |
| Death                  | 0.8% (73)                           | 0.4% (5)                         |
| Life-threatening       | 1.1% (93)                           | 2.0% (29)                        |
| Hospitalisation        | 13.6% (1176)                        | 7.3% (104)                       |
| Disabling              | 0.5% (47)                           | 1.5% (21)                        |
| Congenital anomaly     | 0.2% (15)                           | 0.0% (0)                         |
| Primary reporting source |                                   |                                  |
| Physician              | 47.8% (4136)                        | 69.1% (984)                      |
| Pharmacist             | 5.5% (479)                          | 5.8% (83)                        |
| Other HCP              | 10.5% (911)                         | 6.2% (89)                        |
| Consumer/non-HCP       | 34.1% (2956)                        | 5.7% (81)                        |
| Origin: Germany        | 37.1% (3212)                        | 58.0% (827)                      |
reports. In terms of differences between the ADR profiles of dimethyl fumarate and nicotinic acid, the SOCs “skin and subcutaneous tissue disorders” (OR 0.3 [0.2-0.3]), “musculoskeletal and connective tissue disorders” (OR 0.3 [0.3-0.5]), “vascular disorders” (OR 0.4 [0.3-0.5]) and “cardiac disorders” (OR 0.4 [0.3-0.6]) were more often found in nicotinic acid reports. Conversely, the SOCs “blood and lymphatic system disorders” (OR 15.3 [6.4-36.7]), “infections and infestations” (OR 8.0 [4.0-16.3]) as well as “neoplasms benign, malignant and unspecified (including cysts and polyps)” (OR 24.7 [4.1-150.4]) were more often found in dimethyl fumarate reports (Figure 2).

### 3.3 | Similarities and differences of reported ADRs: Dimethyl fumarate reports vs nicotinic acid reports

#### 3.3.1 | Differences: HLGTs, HLTs and PTs coded only in dimethyl fumarate reports

The most frequently reported HLGT, only assigned to dimethyl fumarate reports, was “demyelinating disorders” (n = 736) (Table 2). In analogy, this finding was also reflected in the finer levels of hierarchy (HLT “multiple sclerosis acute and progressive” [n = 732], PTs “multiple sclerosis relapse” [n = 512] and “multiple sclerosis” [n = 213]). The second most frequently reported HLGT, only presented in dimethyl fumarate reports, was “investigations, imaging and histopathology procedures NEC [not elsewhere classified]” (n = 108). In general, various kinds of neoplasms and gallbladder disorders were reported. Regarding the 10 most coded HLTs, various infections, the HLT “leucocytosis NEC” and HLTs possibly belonging to the underlying disease MS were observed. The same applies to the PT level with “lymphopenia” (n = 777) as most reported PT.

#### 3.3.2 | Differences: HLGTs, HLTs and PTs more often reported with dimethyl fumarate treatment

The HLGTs with the highest ORs for being reported with dimethyl fumarate compared to nicotinic acid treatment were “white blood cell disorders” (OR 89.2 [6.6-1201.4]) and “viral infectious disorders” (OR 27.6 [2.0-373.5]) (only two reports in nicotinic acid reports for both), followed by “haematology investigations (including blood groups)” (OR 14.0 [3.8-52.0]) (eight reports in nicotinic acid reports). Similar results were observed in the HLT analysis with the highest calculated ORs for “leucopenias NEC” (OR 149.8 [2.9-7705.1]) (one report in nicotinic acid reports), followed by “white blood cell analyses” (OR: 51.3 [3.1-835.3]) (two reports in nicotinic acid reports) and “alopecias” (OR: 7.2 [1.2-42.7] (five reports in nicotinic acid reports). In the PT analysis, only “alopecias” (OR: 6.8 [1.0-45.6]) and “gastrointestinal disorder” (OR 5.4 [1.4-20.8]) remained.

### 3.3.3 | Differences: HLGTs, HLTs and PTs less often found in dimethyl fumarate reports

The HLGTs with the lowest ORs for being reported with dimethyl fumarate compared to nicotinic acid treatment were “changes in physical activity” (OR 0.0 [0.0-0.3]) (three reports in dimethyl fumarate reports), “enzyme investigations NEC” (OR 0.1 [0.0-0.1]) (19 reports in dimethyl fumarate reports) and “lipid analyses” (OR 0.1 [0.0-0.2]). In general, the remaining HLGTs, which were more common in nicotinic acid than in dimethyl fumarate reports, mostly represent muscle, metabolic, skin and cardiac diseases. The same applies to the lower-level analysis of the HLT and PT level.

### 3.3.4 | Similarities: HLGTs, HLTs and PTs similarly distributed among dimethyl fumarate and nicotinic acid reports

With regard to similarities of the ADRs among dimethyl fumarate and nicotinic acid reports, the OR closest to 1 was observed for the HLGT “anxiety disorders and symptoms” (OR 0.9 [0.3-2.2]). The same applied to the associated HLT “anxiety symptoms” (OR 1.0 [0.3-3.2]) in the HLT analysis. Two of the 10 HLGTs with ORs closest to 1 belong to the SOC “gastrointestinal disorders”, namely “gastrointestinal signs and symptoms” (OR 0.8 [0.6-1.1]) and “gastrointestinal motility and defecation conditions” (OR 1.2 [0.8-1.9]). With regard to the SOC “gastrointestinal disorders”, the HLTs “diarrhoea (excluding infective)” (OR 1.2 [0.7-1.8]), “flatulence, bloating and distension” (OR 1.4 [0.4-4.3]) and “diabetic signs and symptoms” (OR 0.5 [0.2-1.4]) were detected as similarities in the lower level HLT analysis. Additionally, at the PT level, “vomiting” (OR 0.9 [0.4-1.7]), “diarrhoea” (OR 1.2 [0.7-2.0]) and “flatulence” (OR 0.8 [0.1-4.7]) were similarly distributed among dimethyl fumarate and nicotinic acid reports.

Another two of the 10 HLGTs with ORs closest to 1 belong to the SOC “investigations”: “physical examination and organ system status topics” (OR 1.2 [0.5-3.0]) and “hepatobiliary investigations” (OR 1.3 [0.7-2.5]). Regarding the HLGT “hepatobiliary investigations”, its associated HLT “liver function analysis” (OR 1.3 [0.7-2.6]) and PT “gamma-glutamyltransferase increased” (OR 0.9 [0.3-3.3]) are listed among the 10 HLTS and PTs closest to OR = 1.

### 3.4 | HCA2 receptor expression in mouse organs and results of the Ussing chamber experiments

Similarities in the ADR profile between dimethyl fumarate and nicotinic acid may be mediated by their common target HCA2. Therefore, by using an HCA2 reporter mouse line we evaluated whether organs that are affected by ADRs to dimethyl fumarate and nicotinic acid express HCA2. We found HCA2-expressing cells in the central nervous system, small intestine, colon, liver and lung as well as in
kidney, spleen and brown adipose tissue (Figure 3 and Supporting Information Figure S2). In most tissues, HCA2-expressing cells had the morphology of macrophages but we did not further characterize the cell types.

To explore the role of HCA2 in diarrhoea induced by dimethyl fumarate and nicotinic acid, we used an Ussing chamber approach to investigate whether the drugs would influence electrogenic trans epithelial transport as a possible mechanism underlying diarrhoea. However, while forskolin- and carbachol-induced secretory currents were in the normal range, neither dimethyl fumarate nor nicotinic acid had an acute effect on transepithelial transport in the small intestine or colon of mice (Supporting Information Figure S3), indicating that other mechanisms are involved. Inhibition of sodium reabsorption by amiloride could not unmask any difference in the action of dimethyl fumarate and nicotinic acid.

**FIGURE 2** Number of adverse drug reaction reports per system organ class (SOC) for dimethyl fumarate and nicotinic acid and their calculated odds ratio (± 95% confidence interval [CI]). The upper limit of the CI (150.4) of the SOC “neoplasms, benign, malignant and unspecified (including cysts and polyps)” is extremely high. Hence, it is truncated in the figure (see CIs presented in the labels)

### DISCUSSION

The aim of the present study was to compare the ADR profiles of dimethyl fumarate and nicotinic acid based on ADR reports and to discuss a possible involvement of the HCA2 receptor. The analysis of ADR reports was combined with an investigation of HCA2 in murine organs. The comparison between dimethyl fumarate and nicotinic acid ADR reports showed both similarities and discrepancies.

Flushing is a known HCA2-mediated ADR to both dimethyl fumarate and nicotinic acid.7,13 As such, it stimulated our search for further common and potentially HCA2-dependent ADRs. Concerning the OR analysis, the PT “flushing” (OR 0.4 [0.3-0.5]) was more often reported for nicotinic acid. The analysis includes the combination drug nicotinic acid/laropiprant, which was developed to reduce flushing. However, as it selectively blocks DP1 but not (vasodilatory) EP2 and
### TABLE 2
HLGTs, HLTs and PTs only found in dimethyl fumarate reports, more often found in dimethyl fumarate reports, more often found in nicotinic acid reports and similarly distributed between dimethyl fumarate and nicotinic acid reports

#### HLGT analysis

| Reported only in dimethyl fumarate reports: the 10 HLGTs reported most frequently | Reported more often in dimethyl fumarate reports: the HLGTs with the highest OR and lower CI > 1 | Reported more often in nicotinic acid reports: the 10 HLGTs with the lowest OR and upper CI < 1 | Reported similarly frequent in dimethyl fumarate and nicotinic acid reports: the HLGTs closest to OR = 1 |
|---|---|---|---|
| 1. Demyelinating disorders (n = 736) | White blood cell disorders OR 89.2 [6.6-1201.4] | Changes in physical activity OR 0.0 [0.0-0.3] | Skin appendage conditions OR 1.5 [0.8-2.9] |
| 2. Investigations, imaging and histopathology procedures NEC (n = 108) | Viral infectious disorders OR 27.6 [2.0-373.5] | Enzyme investigations NEC OR 0.1 [0.0-0.1] | Hepatobiliary investigations OR 1.3 [0.7-2.5] |
| 3. Breast neoplasms malignant and unspecified (including nipple) (n = 96) | Haematology investigations (including blood groups) OR 14.0 [3.8-52.0] | Lipid analyses OR 0.1 [0.0-0.2] | Gastrointestinal motility and defecation conditions OR 1.2 [0.8-1.9] |
| 4. Skin neoplasms malignant and unspecified (n = 62) | Infections: pathogen unspecified OR 6.1 [2.3-15.9] | Muscle disorders OR 0.1 [0.1-0.2] | Physical examination and organ system status topics OR 1.2 [0.5-3.0] |
| 5. Gallbladder disorders (n = 34) | Gastrointestinal conditions NEC OR 3.8 [1.6-9.3] | Decreased and nonspecific blood pressure disorders and shock OR 0.2 [0.1-0.5] | Musculoskeletal and connective tissue disorders NEC OR 1.2 [0.5-2.6] |
| 6. Miscellaneous and site unspecified neoplasms malignant and unspecified (n = 28) | | Metabolic, nutritional and blood gas investigations OR 0.2 [0.1-0.5] | Anxiety disorders and symptoms OR 0.9 [0.3-2.2] |
| 7. Reproductive neoplasms female malignant and unspecified (n = 26) | | Epidermal and dermal conditions OR 0.2 [0.2-0.3] | Gastrointestinal signs and symptoms OR 0.8 [0.6-1.1] |
| 8. Respiratory and mediastinal neoplasms malignant and unspecified (n = 24) | | Coronary artery disorders OR 0.3 [0.1-0.9] | Respiratory disorders NEC OR 0.6 [0.3-1.2] |
| 9. Sleep disturbances (including subtypes) (n = 23) | | Sleep disorders and disturbances OR 0.3 [0.1-0.7] | Allergic conditions OR 0.5 [0.3-1.0] |
| 10. Renal and urinary tract neoplasms malignant and unspecified (n = 22) | | Glucose metabolism disorders (including diabetes mellitus) OR 0.3 [0.1-0.9] | |

#### HLT analysis

| Reported only in dimethyl fumarate reports: the 10 HLTs reported most frequently | Reported more often in dimethyl fumarate reports: the HLTs with the highest OR and lower CI > 1 | Reported more often in nicotinic acid reports: the 10 HLTs with the lowest OR and upper CI < 1 | Reported similarly frequent in dimethyl fumarate and nicotinic acid reports: the HLTs closest to OR = 1 |
|---|---|---|---|
| 1. Multiple sclerosis acute and progressive (n = 732) | Leucopenias NEC OR 149.8 [2.9-7705.1] | Myopathies OR 0.0 [0.0-0.2] | Flatulence, bloating and distension OR 1.4 [0.4-4.3] |
| 2. Breast and nipple neoplasms malignant (n = 95) | White blood cell analyses OR 51.3 [3.1-835.3] | Skeletal and cardiac muscle analyses OR 0.0 [0.0-0.1] | Liver function analyses OR 1.3 [0.7-2.6] |
| 3. Lower respiratory tract and lung infections (n = 79) | Alopecias OR 7.2 [1.2-42.7] | Increased physical activity levels OR 0.0 [0.0-0.3] | Physical examination procedures and organ system status OR 1.2 [0.4-3.3] |
| 4. Investigations NEC (n = 70) | Gastrointestinal disorders NEC OR 3.7 [1.4-9.6] | Muscle pains OR 0.0 [0.0-0.1] | Diarrhoea (excluding infective) OR 1.2 [0.7-1.8] |
| 5. Abdominal and gastrointestinal infections (n = 66) | Gastrointestinal and abdominal pains (excluding oral and throat OR 1.8 [1.1-2.9] | Triglyceride analyses OR 0.1 [0.0-0.4] | Anxiety symptoms OR 1.0 [0.3-3.2] |
| 6. Influenza viral infections (n = 56) | | Cholesterol analyses OR 0.1 [0.0-0.4] | Musculoskeletal and connective tissue pain and discomfort OR 0.8 [0.3-2.0] |

(Continues)
prostaglandin receptors, nicotinic acid-induced flushing still develops in a relevant proportion of patients. In relation to the total number of reports (n = 8656), flushing was also frequently present in dimethyl fumarate reports (11.2%; n = 967). However, according to the criteria defined, it was not equally distributed for the two drugs. The proportions of the PT “hot flush” (OR 0.6 [0.3-1.2]) were similar in the reports of both drugs. However, it is not part of the 10 PTs with an OR closest to 1. Overall, flushing only partially presents as a potentially common ADR to dimethyl fumarate and nicotinic acid in our analysis. A possible explanation for this might be a reporting bias. For instance, stimulated reporting of other ADRs such as lymphopenia associated with dimethyl fumarate due to alerts from the medical agencies could have reduced the proportional share of ADR reports about flushing.

Gastrointestinal symptoms were identified as similarities in the ADR profiles of dimethyl fumarate and nicotinic acid at all MedDRA levels. At PT level, several symptoms with an OR close to one were detected, eg, “diarrhoea” (OR 1.2 [0.7-2.0]), “vomiting” (OR 0.9 [0.4-1.7]) and “flatulence” (OR 0.8 [0.1-4.7]). Gastrointestinal ADRs are clinically relevant, as they are, in addition to flushing, a frequent reason for patients to discontinue therapy with dimethyl fumarate or nicotinic acid. HCA2 is located in the gastrointestinal tract.

**TABLE 2 (Continued)**

| HLT analysis |
|----------------------------------|
| Reported only in dimethyl fumarate reports: the 10 HLTs reported most frequently | Reported more often in dimethyl fumarate reports: the HLTs with the highest OR and lower CI > 1 | Reported more often in nicotinic acid reports: the 10 HLTs with the lowest OR and upper CI < 1 | Reported similarly frequent in dimethyl fumarate and nicotinic acid reports: the HLTs closest to OR = 1 |
| 7. Co-ordination and balance disturbances (n = 48) | Circulatory collapse and shock OR 0.1 [0.0-0.7] | Angioedemas OR 0.6 [0.2-1.6] |
| 8. Leucocytoses NEC (n = 42) | Carbohydrate tolerance analyses (including diabetes) OR 0.1 [0.0-0.4] | Allergic conditions NEC OR 0.5 [0.2-1.2] |
| 9. Imaging procedures NEC (n = 38) | Pruritus NEC OR 0.2 [0.1-0.2] | Dyspeptic signs and symptoms OR 0.5 [0.2-1.4] |
| 10. General nutritional disorders NEC (n = 37) | Dermal and epidermal conditions NEC OR 0.2 [0.1-0.3] | Neurological signs and symptoms NEC OR 0.5 [0.3-1.0] |

| PT analysis |
|----------------------------------|
| Reported only in dimethyl fumarate reports: the 10 PTs reported most frequently | Reported more often in dimethyl fumarate reports: the PTs with the highest OR and lower CI > 1 | Reported more often in nicotinic acid reports: the 10 PTs with the lowest OR and upper CI < 1 | Reported similarly frequent in dimethyl fumarate and nicotinic acid reports: the PTs closest to OR = 1 |
| 1. Lymphopenia (n = 777) | Alopecia OR 6.8 [1.0-45.6] | Blood creatine phosphokinase increased OR 0.0 [0.0-0.1] | Decreased appetite OR 1.2 [0.2-7.7] |
| 2. Multiple sclerosis relapse (n = 512) | Gastrointestinal disorder OR 5.4 [1.4-20.8] | Restlessness OR 0.0 [0.0-0.4] | Weight increased OR 1.2 [0.2-6.5] |
| 3. Lymphocyte count decreased (n = 371) | Rhabdomyolysis OR 0.0 [0.0-1.0] | Diarrhoea OR 1.2 [0.7-2.0] |
| 4. Multiple sclerosis (n = 213) | Myalgia OR 0.0 [0.0-0.1] | Thrombocytopenia OR 1.2 [0.2-7.4] |
| 5. Psoriasis (n = 64) | Blood triglycerides increased OR 0.1 [0.0-0.4] | Pain in extremity OR 1.2 [0.2-5.7] |
| 6. Blood test abnormal (n = 58) | Skin burning sensation OR 0.1 [0.0-0.2] | Gamma-glutamyltransferase increased OR 0.9 [0.3-3.3] |
| 7. Influenza (n = 55) | Blood glucose increased OR 0.1 [0.0-0.5] | Back pain OR 0.9 [0.2-5.1] |
| 8. Breast cancer (n = 55) | Circulatory collapse OR 0.1 [0.0-1.0] | Vomiting OR 0.9 [0.4-1.7] |
| 9. Memory impairment (n = 42) | Blood cholesterol increased OR 0.1 [0.0-0.7] | Blood creatinine increased OR 0.8 [0.1-6.4] |
| 10. Stress (n = 42) | Pruritus generalized OR 0.2 [0.1-0.4] | Flatulence OR 0.8 [0.1-4.7] |

Note: The full analysis is presented in the Supporting Information table.
Abbreviations: CI, confidence interval; HLGT, high level group term; HLT, high level term; NEC, not elsewhere classified; OR, odds ratio; PT, preferred term.

**EP4** prostaglandin receptors, nicotinic acid-induced flushing still develops in a relevant proportion of patients. In relation to the total number of reports (n = 8656), flushing was also frequently present in dimethyl fumarate reports (11.2%; n = 967). However, according to the criteria defined, it was not equally distributed for the two drugs. The proportions of the PT “hot flush” (OR 0.6 [0.3-1.2]) were similar in the reports of both drugs. However, it is not part of the 10 PTs with an OR closest to 1. Overall, flushing only partially presents as a potentially common ADR to dimethyl fumarate and nicotinic acid in our analysis. A possible explanation for this might be a reporting bias. For instance, stimulated reporting of other ADRs such as lymphopenia...
However, our experiments with the Ussing chamber gave negative results for both substances, suggesting that dimethyl fumarate and nicotinic acid do not cause diarrhoea and other symptoms by changing transepithelial transport via acute receptor-mediated interaction with the mucosal epithelium (Supporting Information Figure S3). In accordance with this, HCA2 was mainly expressed in subepithelial cells of the gastrointestinal tract (Figure 3). The pathogenesis of gastrointestinal symptoms such as diarrhoea comprises a variety of possible mechanisms and mediators.17,18 One example involves prostaglandins, which not only mediate vasodilation during dimethyl fumarate- and nicotinic acid-induced flushing, but also have propulsive and secretory effects in the gastrointestinal tract.7,19 Although our data do not prove the involvement of HCA2 in diarrhoea, the striking frequency with which similar gastrointestinal symptoms were reported for both drugs suggests that HCA2 might be involved.

We identified “anxiety disorders and symptoms” (OR 0.9 [0.3-2.2]) at the HLGT level and “anxiety symptoms” (OR 1.0 [0.3-3.2]) as one of the similarly distributed ADRs at the HLT level for dimethyl fumarate and nicotinic acid. However, both underlying indications – MS and vascular diseases secondary to dyslipidemia – may have influenced this observation because serious diseases are often associated with an increased incidence of anxiety.20,21 In clinical trials, anxiety has been observed as a rare ADR to the combination product nicotinic acid and laropiprant.22 However, no increased risk of psychiatric ADRs has been identified for dimethyl fumarate.23 Therefore, further research seems warranted. HCA2 is present in microglial cells of all brain areas and might mediate neuroprotective effects of dimethyl fumarate in patients with MS.2,24 As glial cells are involved in the pathogenesis of anxiety disorders,25 HCA2 activation might be a possible mechanism.
Increased liver enzymes were identified as similarly distributed to dimethyl fumarate and nicotinic acid in our analysis. In placebo-controlled studies, elevated liver aminotransferases were observed, but no hepatic failure was reported during the treatment of MS with dimethyl fumarate. The mechanism potentially underlying dimethyl fumarate-associated hepatotoxicity is not known, but it may be immune mediated. Involvement of the CYP450 system in hepatotoxic effects seems unlikely as dimethyl fumarate is extensively metabolized by esterases. Likewise, studies have reported that elevated liver aminotransferases are associated with nicotinic acid treatment. In particular, sustained-release (SR) nicotinic acid, which causes less cutaneous flushing than immediate release (IR) formulations, induced the formation of hepatotoxic pyrimidine intermediates. HCA2 is present in human and rodent liver tissue. We found HCA2 expression in mouse liver, probably in Kupffer cells of liver sinusoids (Figure 3). Overall, in the present analysis hepatic disorders were identified as similarities in the ADR profiles of dimethyl fumarate and nicotinic acid. However, HCA2-independent pathomechanisms might represent alternative explanations for these similarities.

Blood and lymphatic system disorders were more often found in dimethyl fumarate reports at the HLGT and HLT level. “Lymphopenia” was the most frequently reported PT only coded in dimethyl fumarate reports (n = 777). Lymphopenia and leucopenia are listed as common ADRs to dimethyl fumarate. In contrast, literature reports of nicotinic acid-induced haematopoietic disorders are rare. The exact mechanism underlying dimethyl fumarate-induced lymphopenia is unclear. The disparate frequency of ADR reports in which lymphopenia was reported during dimethyl fumarate and nicotinic acid treatment argues that HCA2 is not involved. Instead, it may be linked to inhibition of the NF-κB pathway. Lymphopenia is of clinical significance, as it increases the risk of serious opportunistic infections. In clinical studies, infections developed more frequently during dimethyl fumarate therapy than with placebo. Regarding nicotinic acid-associated infections, the literature is inconsistent. In two recent clinical studies, significantly higher infection rates were observed for nicotinic acid alone and in combination with laropiprant than for placebo. However, this had not been reported in previous studies and is considered controversial. Since HCA2 is expressed on immune cells such as macrophages and neutrophilic granulocytes and mediates numerous anti-inflammatory effects, receptor activation might promote infections. Overall, our analyses showed that infections were reported more often for dimethyl fumarate, suggesting that HCA2 is not involved.

In nicotinic acid reports, there were more reports concerning impaired glucose tolerance at all MedDRA levels than in dimethyl fumarate reports. Elevated fasting glucose is a known ADR to nicotinic acid. In addition, a 34% higher risk of developing diabetes compared to placebo or standard care was found in a meta-analysis. As a mechanism of nicotinic acid-induced hyperglycaemia, a reduction in hepatic insulin sensitivity has been discussed. Furthermore, recent studies have suggested an involvement of HCA2 in glucose metabolism. If HCA2 mediates the hyperglycaemic effect of nicotinic acid, one would expect a similar proportion of respective ADR reports for dimethyl fumarate. However, consistent with the literature, we could not find this in our analysis. A possible explanation here might be additional effects of dimethyl fumarate on glucose metabolism through other metabolic pathways. Activation of NRF2 by dimethyl fumarate may increase insulin sensitivity. Moreover, there are differences in the patient populations receiving nicotinic acid and dimethyl fumarate with regard to age and comorbidities. Patients who received nicotinic acid were usually older and suffered more from diabetes or pre-diabetes, which in combination with nicotinic acid might lead to hyperglycaemia.

The strengths of our study using data from the spontaneous reporting system are a large number of cases with real-world data and the inclusion of high-risk groups such as persons with several comorbidities. Another strength is the possibility of detecting rare ADRs and ADRs with long latency, in contrast to clinical studies, which usually involve a small number of cases and a short period of observation. The limitations of our study are differences in the patient populations in terms of age, comorbidities and co-medication. Patients who received nicotinic acid were older and suffered from more cardiovascular disease, which may have affected the ADRs reported and the reporting itself. Furthermore, we did not analyse treatment duration, time to onset of ADRs or the quality of reports, which may provide information about causality. Among the inherent limitations are varying degrees of documentation in the reports, under-, preferential and stimulated reporting, and not being able to calculate ADR frequencies due to lack of exposure data.

In conclusion, our analysis of spontaneous reports of suspected ADRs to dimethyl fumarate and nicotinic acid revealed mainly gastrointestinal symptoms as potentially common HCA2-mediated ADRs. How HCA2 activation triggers diarrhoea and other gastrointestinal symptoms remains unclear, as our experimental data did not provide evidence for an effect on the electrogenic transepithelial transport. In addition, anxiety was identified as a potentially common ADR with possible involvement of HCA2. In contrast, lymphopenia or glucose tolerance disorders were identified as drug-specific for dimethyl fumarate or nicotinic acid, respectively, making involvement of HCA2 unlikely. To our knowledge, this is the first study comparing two HCA2 agonists using a large data set of spontaneous reports of suspected ADRs. In view of numerous metabolic and anti-inflammatory effects, more diseases might be treated with HCA2 agonists such as dimethyl fumarate and nicotinic acid in the future. In this respect a better understanding of the underlying mechanisms of the desired effects and ADRs could be helpful.

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COMPETING INTERESTS
There are no competing interests to declare. The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

CONTRIBUTORS
Study concept and design (B.S., M.Schw.), acquisition of data (D.D., J.K.), analysis and interpretation of data (D.D., B.S., M.Schm., R.P., M.Schw., M.B.), and drafting the manuscript and the final approval of the version to be published (D.D., B.S., M.Schm., R.P., M.Schw., M.B., S.O.).

DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR
This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the BJR guidelines for Design and Analysis, and Animal Experimentation, and as recommended by funding agencies, publishers and other organisations engaged with supporting research.

DATA AVAILABILITY STATEMENT
Research data are not shared.

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