ELSEVIER

Olfactory drug effects approached from human-derived data

Jörn Lötsch[1,2], Claudia Knothe[1], Catharina Lippmann[2,3], Alfred Ultsch[3], Thomas Hummel[4] and Carmen Walter[1]

[1] Institute of Clinical Pharmacology, Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany
[2] Fraunhofer Project Group Translational Medicine and Pharmacology (IME-TMP), Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany
[3] DataBionics Research Group, University of Marburg, Hans-Meerwein-Strabe, 35032 Marburg, Germany
[4] Smell & Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany

The complexity of the sense of smell makes adverse olfactory effects of drugs highly likely, which can impact a patient's quality of life. Here, we present a bioinformatics approach that identifies drugs with potential olfactory effects by connecting drug target expression patterns in human olfactory tissue with drug-related information and the underlying molecular drug targets taken from publically available databases. We identified 71 drugs with listed olfactory effects and 147 different targets. Taking the target-based approach further, we found additional drugs with potential olfactory effects, including 152 different substances interacting with genes expressed in the human olfactory bulb. Our proposed bioinformatics approach provides plausible hypotheses about mechanistic drug effects for drug discovery and repurposing and, thus, would be appropriate for use during drug development.

Introduction

The first scientific report of a drug effect on olfaction dates back more than 160 years, when Fröhlich reported a significant weakening of his sense of smell after he had taken morphine 80 mg [1]. Since then, several further effects of drugs on the human sense of smell have been reported [2,3]. However, despite the long history of the study of olfactory drug effects in humans, systematic evidence from controlled studies has remained remarkably sparse (Table 1). Indeed, most information about olfactory drug effects has been acquired from single clinical case reports [2–4]. Nevertheless, a recent analysis of a pharmacovigilance database clearly indicated that smell abnormalities are common complaints of patients receiving pharmacological treatment [5]. Therefore, improving patient care via developing better medicines as a main task of clinical pharmacology [6] should include a regard for adverse olfactory effects.

The identification of such effects is still a challenging task. First, testing drug effects on olfaction is not included in standard drug development requirements. Moreover, a systematic assessment in controlled studies to increase the body of evidence exceeds economic practicability. Therefore, a careful preselection of candidate drugs possibly interfering with olfaction is needed. Given that the olfactory system shows species-specific differences [7], a human approach would be required [8]. Therefore, here we summarize current knowledge of the effects of drugs on human olfaction, merging clinical and human molecular biology evidence with knowledge of drugs and their targets to obtain details of olfactory drug effects from currently available information.

Relevance of drug effects on human olfaction

Humans are microsmatic [9], having only a poor sense of smell and expressing approximately 400 olfactory receptors [10,11]. This is in contrast to rodents, which are macrosmatic [9], expressing more than 1000 olfactory receptors [10]. This suggests a reduced importance of olfaction in human life compared with other mammals, which is likely to have contributed to its neglect as an adverse drug effect during drug development. Nonetheless, olfactory disorders are a common reason for patients to consult a doctor; for example,

Corresponding author: Lötsch, J. (j.loetsch@em.uni-frankfurt.de)

http://dx.doi.org/10.1016/j.drudis.2015.06.012

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

TABLE 1

Published studies of drug effects on human olfaction (sorted by year of publication).

Study refs	Drug studied	Influence on olfaction
[75]	Apomorphine	None
[35]	Remifentanil	Reduced
[76]	Caroverine	Improved
[77]	Alpha lipoic acid	Improved
[53]	Citrate buffer	Improved
[78]	Sildenafil	Reduced
[79]	Pentoxifylline	Improved
[80]	Herbal mix	None
[81]	Minocycline	None
[82]	Vitamin A (systemic)	None
[83]	Tetrahydrocannabinol	Reduced
[36]	Fluconazole	None

an estimated 80,000 patients annually in German-speaking countries present to their doctor with olfaction-related complaints [12]. This emphasizes the important role of the sense of smell in human everyday life that is not restricted to professionals who rely on their sense of smell, such as chefs, perfumers, or oenologists. The sense of smell conveys the flavor perception of food and drink [13], and warns us of danger (e.g., tainted food, smoke, fire, and poisons). Fragrances have been shown to affect the hedonic tone of dreams [14], and are involved in mother–child and sexual relations (e.g., [15]). In line with these functions, scientists have repeatedly shown that olfaction is an important component of the quality of life [16–18], which most humans only realize when their sense of smell is impaired. Of 750 patients from the University of Pennsylvania Smell and Taste Center, 68% reported a decrease in their quality of life [19]. Olfactory dysfunction is perceived by more than 40% of patients as a cause of a reduced mood [20]. Smell abnormalities are also among common complaints of patients during pharmacological treatments [5]. Given the important role of olfaction in human life, current efforts at personalized therapy strategies [6] should include olfactory effects.

Measurement of human smell function

Olfactory function is quantified by means of psychophysical, electrophysiological, and psychophysiological tests. The first two categories are the most commonly used. Psychophysical olfactory tests assess the three main components of olfactory function comprising: (i) the perception of odors at low concentrations, which is the odor threshold; (ii) the distinction of different smells, which is odor discrimination; and (iii) the ability to name or associate an odor, which is odor identification. Current smell tests include separate sets for the assessment of each of these components [21] or parts thereof [22]. Electrophysiological olfactory tests assess cortical evoked potentials or local recordings from the olfactory epithelium (i.e., electro-olfactography; EOG [23]) following intranasal administration of olfactory stimuli. Psychophysiological tests assess cardiovascular changes or changes in inhaling air associated with the subjects' exposure to odorants. Assessments of olfactory drug effects have to consider that olfactory functions decrease with increasing age of the subjects [24,25] and are, on average, better in the female sex [26], although this is also affected by the estrous cycle [27].

Detecting traces of olfactory drug effects in clinical drug-related data

Influences on olfactory function can result in decreased smelling acuity, called hyposmia or anosmia [28] according to the existence of residual or absent olfactory function, respectively, or in the distorted smelling of common odorants (parosmia). Compilations of single case reports [2–4] provided more than 40 drugs that were associated with altered human olfaction. Further drugs were added from case reports not included in these reviews (i.e., morphine [1], 5-fluorouracil [29], pyrazinamide [30], propylthiouracil [31], carbimazole, clomipramine, methimazole, methylthiouracil, ticarcillin [32], ciprofloxacin, diltiazem, felodipine, interferon-alfa [33], and sevoflurane [34]). Pursuing anecdotal information from single cases can be positive, as exemplified by the verification of a single case report [1] about opioid effects on olfaction in a controlled study [35]. They can also be negative, such as the results of a controlled study on anecdotally reported effects of antimycotics on olfaction [36]. Information can be gathered from larger samples in pharmacoepidemiological analyses, such as a recent query of the Italian spontaneous adverse drug reaction-reporting database [5]. Using this, we identified a further six drugs as being associated with olfactory complaints. As an alternative to pharmacovigilance approaches, a recent cross-sectional assessment used olfactory testing of 1006 outpatients from a general practice. Of the 168 different drugs queried from the patients' records, six were taken by a sufficiently large enough number of patients to qualify for statistical analysis [37]. At the drug-centered level of that analysis, levothyroxine was found to be positively associated with a higher olfactory test score. This fits with the case report of a negative effect of the thyreostatic propylthiouracil on olfaction [31]. Together with the seven drugs for which positive evidence has already been obtained from larger studies (Table 1), we report here on a total of 71 drugs (Table 2) that can be suggested to possibly or probably alter the sense of smell in humans, based on published reports.

Querying drug targets in the context of reported olfactory drug effects

Given that drug effects result from interaction of drug molecules with molecular targets, it seems more logical to base our association analysis on drug targets than on drugs or drug classes. For example, the approximately 400 human olfactory receptors [38,39] are G protein coupled (G_s or the olfactory receptor specific G_{olf} [40]), which is linked to adenylyl cyclase. Receptor activation eventually leads to an intracellular increase in cAMP, which targets olfactory-specific ion channels and is degraded by phosphodiesterases. Therefore, drugs interfering with this cascade, such as opioids or xanthines, could modulate olfactory signaling [41]. The olfactory system comprises many different molecular components and neurotransmitter-mediated signaling [42,43], which suggests the need to analyze targets to identify olfactory drug effects.

A target-based approach is suggested by increasing evidence that many drugs address targets other than from their main mechanisms of action. Specifically, many drugs lack complete specificity

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

TABLE 2

A list of 71 drugs that reportedly modulate human olfaction[a].

Drug name	CAS	Drug name	CAS	Drug name	CAS
Aldesleukin	85898-30-2	Doxycycline	564-25-0	Pentoxifylline	6493-05-6
Amiodarone	1951-25-3	Enalapril	75847-73-3	Phenylephrine	59-42-7
Amlodipine	88150-42-9	Felodipine	72509-76-3	Pirbuterol	38677-81-5
Amoxicillin	71447-36-4	Flunisolide	3385-03-3	Pravastatin	81093-37-0
Amrinone	60719-84-8	Flurbiprofen	5104-49-4	Promethazine	38878-40-9
Atorvastatin	134523-03-8	Fluorouracil	51-21-8	Propylthiouracil	51-52-5
Azithromycin	83905-01-5	Gemfibrozil	25812-30-0	Pyrazinamide	98-96-4
Beclometasone	4419-39-0	Gentamicin	1403-66-3	Remifentanil	132875-61-7
Bromocriptine	25614-03-3	Interferon alfa	99210-65-8	Rimantadine	13392-28-4
Carbimazole	22232-54-8	Isotretinoin	56573-65-0	Roxithromycin	80214-83-1
Caroverine	23465-76-1	Kanamycin	8063-07-8	Scopolamine	226562-00-1
Chlorhexidine	55-56-1	Levodopa	72573-00-3	Sevoflurane	28523-86-6
Cholestyramine	11041-12-6	Levofloxacin	100986-85-4	Sildenafil	139755-83-2
Cimetidine	51481-61-9	Levothyroxine	51-48-9	Sodium citrate	68-04-2
Ciprofloxacin	85721-33-1	Lipoic acid	62-46-4	Streptomycin	12672-24-1
Citric acid	77-92-9	Lovastatin	74133-25-8	Sumatriptan	103628-46-2
Clarithromycin	81103-11-9	Methimazole	60-56-0	Terbinafine	91161-71-6
Clofibrate	637-07-0	Methylthiouracil	56-04-2	Terazosin	63590-64-7
Clomipramine	303-49-1	Morphine	57-27-2	Tetrahydrocannabinol	5957-27-7
Cocaine	50-36-2	Moxifloxacin	354812-41-2	Thiamazole	60-56-0
Corticosteroids[b]	–	Nifedipine	101539-70-2	Ticarcillin	34787-01-4
Cytarabine	147-94-4	Ofloxacin	100986-85-4	Tocainide	41708-72-9
Diltiazem	42399-41-7	Oxymetazoline	1491-59-4	Verapamil	56949-77-0
Doxazosin	74191-85-8	Pentamidine	6823-79-6		

[a] The list was assembled from case reports, pharmacovigilance, pharmacoepidemiology, and cross-sectional assessments, of which many had been summarized previously [2,3]. The Chemical Abstracts Service (CAS) numbers (http://www.cas.org) were queried in November 2014 from the DrugBank database (version 4.1 [45]) at http://www.drugbank.ca.
[b] "Corticoids" represents the drug group name, comrising several of its members.

for their main target, on which drug classifications are based and which is considered in a drug-based approach to olfactory drug effects; therefore, these could contribute to clinical effects, including adverse effects. Hence, including all known targets of a drug in the association analyses of its effects on olfaction provides a more flexible approach compared with a drug- or drug class-based approach that considers only the main drug targets; using the former approach makes clinical effects mechanistically explicable at a broad scale and, thus, usable for drug development.

The target-based approach could benefit from developments in informatics, knowledge discovery, and data-mining methods that enable one to access detailed knowledge about the function of gene products [44] and their interaction with drugs. In this field, the publicly available DrugBank database [45] is becoming a gold standard. It currently lists 7740 drug entries (November 2014) for which a total of 2109 unique targets were queried for the present analysis. This enabled us to connect drug-related information from in humans with molecular drug targets, as discussed below.

Associating drug targets with olfactory effects

Here, we demonstrate a target-based approach to the identification of potential olfactory drug effects using clinical data. In a cross-sectional assessment in 1006 outpatients [37], the 168 different drugs taken by the patients addressed a total of 323 different targets, as queried from the DrugBank database at http://www.drugbank.ca (version 4.1 [45]), of which 32 targets were addressed by medication in a sufficiently large number of patients to qualify for statistical analysis [37]. This analysis identified the thyroid hormone receptors THRA1* and THRB1 as being positively associated with a higher olfactory score, which fits with the identification of levothyroxine in the same cohort (see above; [46]). However, a further finding was the association of antagonistic targeting of the adrenoceptor α_{1A} (ADRA1A) with a higher olfactory score. This target was addressed by several drug classes, including α_1 adrenoceptor-blocking agents, as well as further drugs, such as antidepressants (e.g., amitriptyline, doxepin, or imipramine). Hence, its identification was possible with a target-based but not a drug-based approach.

* For consistency, we use the gene name also when referring to the target protein of a drug. A common nomenclature of proteins is also conferred via UniProt IDs (http://www.uniprot.org). Gene names and UniProt IDs are interconvertible, for example, via the DAVID database ([46]; http://david.abcc.ncifcrf.gov/conversion.jsp). The gene name was preferred to the UniProt ID because the latter is less intuitive, for example the gene name *ACE* refers to its, product angiotensin I converting enzyme, of which the UniProt ID is P12821.

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

From a DrugBank [45] query, ADRA1A emerged as the most frequently addressed target among all 147 targets (Table S1 in the supplementary material online) addressed by the 71 drugs reportedly influencing human olfaction (Table 2). The repeated appearance of this target in two independent analyses points at its olfactory relevance. Of note, the drug list ($n = 71$) was not amended from the above-mentioned first finding of ADRA1A as a relevant target and, therefore, its second appearance in this olfactory context is independent from its first appearance. A role of ADRA1A receives further support from molecular evidence showing that adrenergic activation enhances the inhibitory transmission in the olfactory system (i.e., activation of α_1 increases the GABAergic inhibition of mitral cells in the olfactory bulb) [47–49]. This also agrees with the anecdotal observation of a reversible smell disturbance following administration of the α-adrenoceptor agonist midodrine [50]. When accepting ADRA1A from this line of evidence as an olfactory-relevant drug target, a further DrugBank [45] query found a total of 91 drugs listed as interacting with the ADRA1A receptor (Fig. 2) and possibly qualifying as candidates for drug effects on human olfaction.

Identifying drug targets in human olfactory tissues

In addition to analyses of traces of olfactory effects in human drug-related data, hypotheses for prospective controlled studies can also be based on the expression of drug targets in anatomical structures known to be involved in olfaction. A primary candidate tissue is the olfactory bulb, which is a main processing and relay component for olfactory information. The drug targets expressed in the bulb were obtained from the intersection of relevant sets of drug targets (Fig. 3). Specifically, the set of all drug targets ($n = 2109$) listed in the DrugBank database [45] and the set of targets ($n = 147$; Fig. 1) of drugs reportedly modulating human olfaction based on pharmacovigilance, pharmacoepidemiology, and cross-sectional assessments, were intersected with the set of genes ($n = 231$ [51]) that have been shown to be expressed in the human olfactory bulb based on proteomics [52] and mRNA analyses [51]. This intersection analysis identified 83 drug targets as expressed in the human olfactory bulb (Table S2 in the supplementary material online), of which only two [mitochondrial malate dehydrogenase 2 (MDH2) and glutathione S-transferase pi 1 (GSTP1)] have been shown so far to modulate human olfaction. According to the DrugBank database [45], MDH2 is addressed by NADH and citric acid, of which the latter has been shown to improve olfactory function as a component of sodium citrate buffer [53]. The effect was mechanistically attributed to decreasing nasal mucus. However, the present knowledge of the gene expression pattern in the human olfactory bulb enables us to consider a direct interaction with a protein expressed there. GSTP1 is targeted by several substances, such as hydroxycysteine, carboxymethylenecysteine, clomipramine, and canfosfamide (i.e., mucolytics, antidepressants and antineoplastics), belonging to drug classes that have attributed olfactory effects. Furthermore, for the targets expressed in the human olfactory bulb, a further 152 drugs could be queried (Table S3 in the supplementary material online).

Unfortunately, other human tissues have not yet been analyzed for gene expression. This would be desirable for the olfactory epithelia as the first neuron of the olfactory system or for the piriform cortex as a well-established cerebral component of the olfactory system [54]. Although assessments of human tissue mainly from postmortem probes [51,52,55] or from residual material following surgery [51] are possible, the olfactory system has not been a focus so far. Translating expression evidence from laboratory animals is not ideal, given the differences in expression patterns among mammals [8], such as the number of olfactory receptors (human, 387 receptors; mouse, 1035 receptors; and rat, 1207 receptors [10]) and the number of glomeruli in the olfactory bulb, where the large number of glomeruli in humans (>5000) contrasts with the approximately 1800 glomeruli in mice [56].

A systems-biological analysis of drug effects on olfaction

In a genomic era, the knowledge of drug targets involves the knowledge of their coding genes. This can be exploited for a systems biological analysis using global knowledge of the roles of genes in an organism as represented in the Gene Ontology (GO) knowledge base [57]. In this database, this knowledge is formulated using a controlled vocabulary of GO terms (categories) to which the genes are annotated [58,59]. GO terms are related to one another by 'is-a', 'part-of', 'has-a', and 'regulates' relations, forming a polyhierarchy. Particular biological roles exerted by the targets of the drugs with reported olfactory effects, among all drug targets, were found by over-representation analysis (ORA, $P < 0.01$ Bonferroni α corrected; for further details, see [60]). From this analysis, we highlighted six biological processes as being characteristic for those drugs, among all drugs, that affect human olfaction [i.e., processes related to transport,. such as (i) monoamine transport (GO:0015844) and (ii) ion transport (GO:0006811), in particular that of Ca^{2+} (GO:0006816), and processes related to (iii) signaling (GO:0023052), including (iv) cell communication (GO:0007154), (v) single organism signaling (GO:0044700) and (vi) G protein-coupled receptor signaling pathway (GO:0007186), the latter particularly pointing at to 'adrenergic signaling pathway' and 'serotonin receptor signaling pathway' along the GO hierarchy (details not shown)]. The structure of such a polyhierarchy of terms is explained in detail elsewhere [60], and the precise definition of the GO terms can be obtained using the AmiGO search tool for GO at http://amigo.geneontology.org/ [61]. These results are biologically plausible and supported by molecular evidence, such as the role of serotonergic signaling [62], the importance of calcium ion channels that are involved in olfactory receptor signaling [43], or the above-mentioned molecular mechanism of adrenergic pathways.

Opportunities and challenges

Olfactory drug effects could be approached from human-derived databases by merging several lines of information (Fig. 4). These include: (i) information acquired in the specific olfactory context obtained from clinical observations or human experimental studies; (ii) information acquired in any context, rarely with an olfactory focus, about the targets of drugs; and (iii) information acquired in an often olfactory context obtained from gene expression profiling of human tissue relevant to olfactory function. The availability of several lines of evidence opens the opportunity to maximize the informational basis for a focused systematic search for drugs possibly affecting olfaction. This could detect drugs with potential adverse effects, which have to be considered in

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

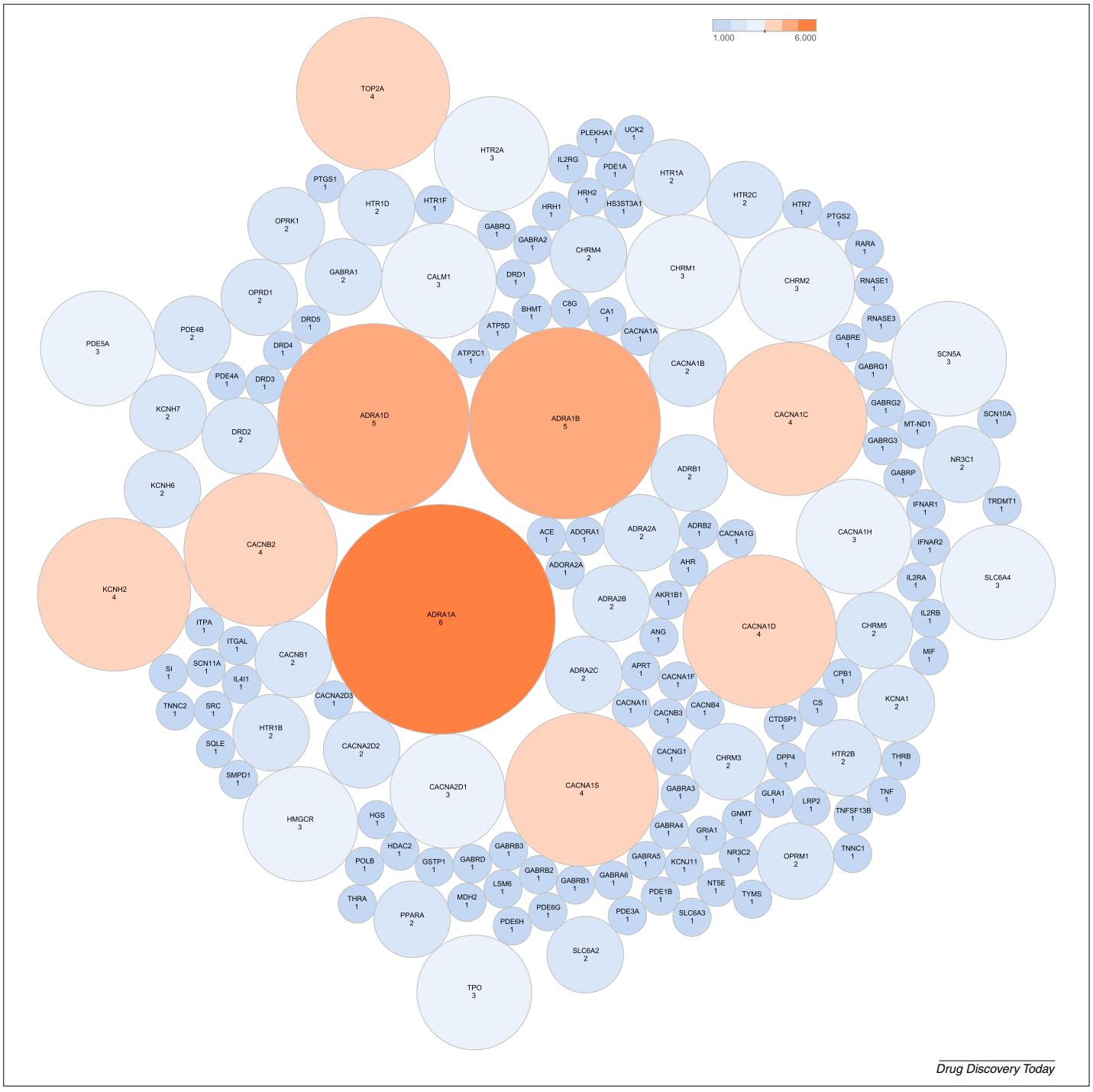

FIGURE 1

Graph displaying as circles the 147 different targets, represented via the names of their coding genes (see Table S1 in the supplementary material online), of the 71 drugs (Table 2, main text), for which effects on human olfaction had been reported. The diameters of the circles are proportional to the number of drugs, among the 71 drugs, by which the particular targets are affected, according to a query of the DrugBank database (version 4.1 [45]) at http://www.drugbank.ca in November 2014. The color code (top right) ranges from blue (one single drug affecting the target) to orange (six drugs affecting the target). The number of drugs addressing a target is also given below the (gene) name of the target. Of note, the adrenoceptor α_{1A} (ADRA1A) was the target that was affected by the largest number of drugs reportedly modulating human olfaction.

personalized therapy strategies, or in the sense of drug repurposing or discovery aimed at cures of olfactory loss, for which therapy options are still limited [63,64].

A challenge associated with detecting traces of drug effects on the human sense of smell is the proof of mechanistic causality. The presence of drugs with changes in olfactory function or the presence of their targets in olfactory tissues merely provide a starting point for the search for a causal relation rather than the end of this search. A target shared among drugs associated with olfactory effects is not necessarily causally involved; each drug could independently alter olfaction via another target. Moreover, olfactory loss is a symptom of various diseases, both of the nasal

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

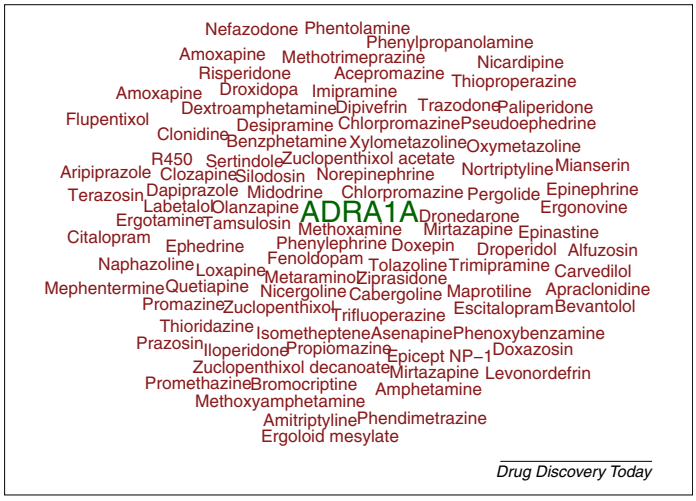

FIGURE 2

Drugs that target the adrenoceptor alpha 1A (ADR1A1) according to a query of the DrugBank database (version 4.1 [45]) at http://www.drugbank.ca in November 2014.

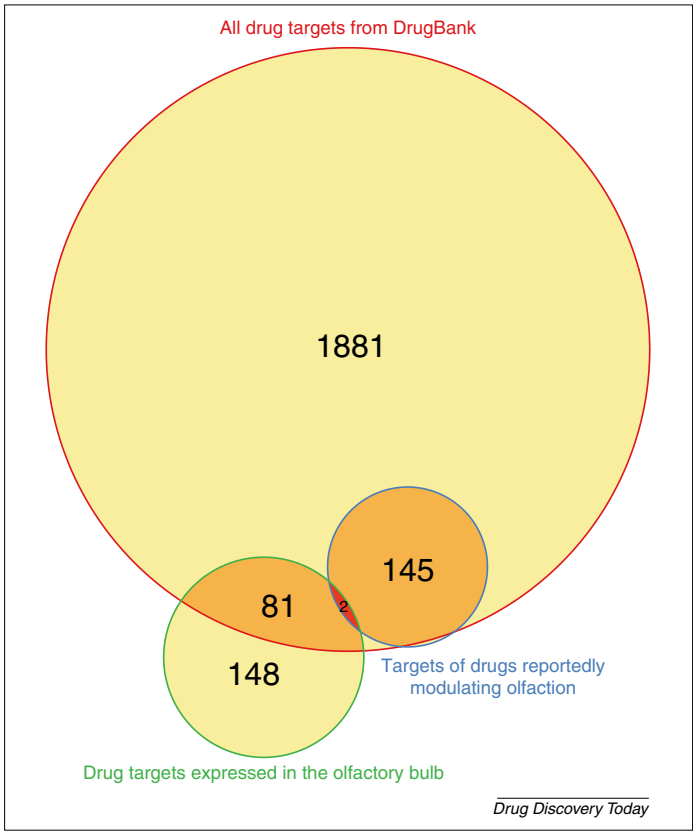

FIGURE 3

Venn diagram [75] showing the intersections between the sets of: (i) drug targets (2109, red margin) queried from the DrugBank database [45]; (ii) the targets of drugs reportedly modulating human olfaction (147 genes, blue margin, for details see Table S1 in the supplementary material online) that have been assembled from case reports, pharmacovigilance, pharmacoepidemiology, and cross-sectional assessments; and (iii) the expression pattern of the human olfactory bulb (231 genes and/or targets, green margin) as published previously [51].

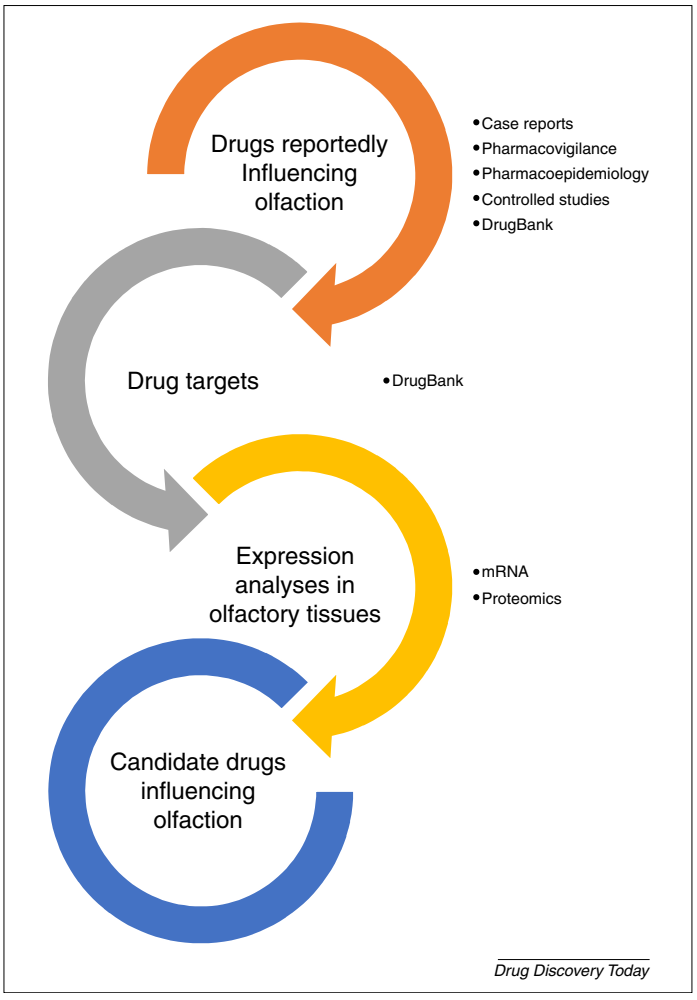

FIGURE 4

Schematic workflow of the identification of potential drug effects on olfaction. For either drugs reportedly influencing human smell perception or tissues relevant for the human sense of smell, drug targets are identified using publicly available information accumulated in knowledge databases, such as the DrugBank database [45]. This information can be complied into candidate drugs that, based on molecular or clinical evidence, potentially modulate the human sense of smell. This evidence can be exploited either for avoiding adverse effects in individualized therapy strategies or for finding cures for olfactory loss.

cavity and the central nervous system. Examples include epilepsy, migraines, hypothyroidism, schizophrenia, infections, and cancer [2]. Therefore, the drug effect on olfaction has to be separated from a disease effect on olfaction, which often seems possible based just on association analyses. Hence, experimental co-information from molecular and preclinical sources is still vital for analyzing the biological plausibility of the associations as well as the causality between the administration of a drug and the observed olfactory loss, albeit in a bedside-to-bench direction that obtains its principal information from human data [65]. Local drug availability and target expression have to be included in these analyses. Finally, the analyses rely on external information and crucially depend on the accuracy and completeness of the queried databases or published gene expression lists.

A further opportunity lies outside the present focus on drug effects on human olfaction. The approach followed here can be applied to almost any drug effect based on human evidence. In

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

particular, by merging information about drug effects, drug targets, including more than the drug class definition, implicitly provide expression patterns and systems biological roles of the gene products targeted by the effective drugs. This opens the way for the inclusion of preclinical data for interpretation of the effects at the molecular level. The methodology described here provides a comprehensive approach to drug discovery and repurposing, or to individualized therapy that considers adverse effects on a broad mechanistic basis.

A challenge emerging from the present approach of an enhanced identification of drugs that affect human olfaction is the judgment of the clinical consequences of newly discovered olfactory drug adverse effects. The question rises whether a thus-identified drug should become contraindicated in patients in whom olfaction has a particular importance, such as the above-mentioned chefs or perfumers. Although in chronic treatment, the use of these drugs might be discouraged, in acute treatment a decrease in olfactory function might be acceptable, although only when the effect is reversible. This poses a challenge for clinical pharmacological research because systematic assessments of the reversibility of olfactory drug effects are sparse. For most drugs found in a database analysis to affect olfaction, these events have been labeled as transient conditions, although several cases were found where the adverse effect appeared to be permanent [5]. Reversibility can be expected for straight-forward primary or secondary olfactory drug effects, defined previously as comprising alterations of information transmission and processing within the olfactory system or of inhibitions of the access of odorants to olfactory sensors, such as following drug-induced modification of nasal mucus [5]. However, as discussed in the literature [5], permanent effects of macrolides, for example, have been hypothetically assigned to a damage of sensory nerves in at least one of the chemosensory systems contributing to the perception of food (i.e., the trigeminal, gustatory, and olfactory systems) [66], with the result of altered interplay between them that can lead to permanent decrease in olfactory acuity. However, the reversibility of olfactory loss can be enhanced, for example, by exposure to odors shown to modulate the regenerative capacity olfactory receptor neurons (e.g., [67,68]). Plasticity in the olfactory system has been shown not only in animals [69], but also after repeated exposure of human subjects to androstenone [70] or coumarin [71]. The positive influence of exposure to odors on odor sensitivity might relate not only to changes at the level of the olfactory epithelium, but also to changes at the level of the olfactory bulb, or at even higher levels of processing [72]. This is exploited in 'olfactory training', which has been shown to improve olfactory function in humans [72–74], which might point at a novel therapeutic option for apparently persisting drug-induced olfactory adverse effects.

Concluding remarks

Drug effects on olfaction are common complaints of patients taking pharmacological treatment. Current evidence includes 71 drugs and 147 drug targets, of which only seven positive findings (drugs) originate from larger studies, on the background of a total of only 12 randomized controlled trials on olfactory drug effects. The repeatedly and consistently shown relevance of the sense of smell for many facets of human life clearly supports the systematic assessment of olfactory drug effects. This is particularly important in the era of individualized therapy, where quality of life becomes increasingly relevant. Drug effects on olfaction are not part of standard drug development requirements and, therefore, their systematic assessment exceeds economical practicability. Their detection has to exploit available data, preferably directly from human sources, given the known species-specific differences that exist in olfactory physiologies. In our study, we have shown several ways in which this information can be obtained. However, our findings need to be supported by molecular mechanistic evidence, which could be obtained from animal experiments [65]. Our analysis further demonstrated that association assessments should be done on drug targets rather than on drug classes. Suitable sources of information and bases for hypotheses needed for controlled studies can be identified from human data comprising pharmacovigilance, pharmacoepidemiology, and cross-sectional assessments as well as expression data from human olfactory tissues, although these are still incomplete.

Acknowledgments

This research received funding from the Else Kröner–Fresenius Foundation (EKFS), Research Training Group Translational Research Innovation – Pharma (TRIP, J.L.) and from the Landesoffensive zur Entwicklung wissenschaftlich-ökonomischer Exzellenz (LOEWE, J.L.), Schwerpunkt: Anwendungsorientierte Arzneimittelforschung. The funders had no role in method design, data selection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2015.06.012.

References

1 Fröhlich, R. (1851) Ueber einige Modificationen des Geruchsinnes. *Akad. Wissenschaft. Wien Math. Nat.* 6, 322–328
2 Doty, R.L. and Bromley, S.M. (2004) Effects of drugs on olfaction and taste. *Otolaryngol. Clin. North Am.* 37 (6), 1229–1254
3 Henkin, R.I. (1994) Drug-induced taste and smell disorders. Incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Saf.* 11, 318–377
4 Henkin, R.I. (1986) Drug effects on smell and taste. In *Pharmacology in Medicine: Principles and Practice* (Pradham, S.N *et al.* eds), pp. 748–753, SP Press
5 Tuccori, M. *et al.* (2011) Drug-induced taste and smell alterations: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. *Drug Saf.* 34, 849–859
6 Birkett, D. *et al.* (2010) Clinical pharmacology in research, teaching and health care: considerations by IUPHAR, the International Union of Basic and Clinical Pharmacology. *Basic Clin. Pharmacol. Toxicol.* 107, 531–559
7 Porter, J. *et al.* (2007) Mechanisms of scent-tracking in humans. *Nat. Neurosci.* 10, 27–29
8 Lötsch, J. and Hummel, T. (2015) Cannabinoid-related olfactory neuroscience in mice and humans. *Chem. Senses* 40, 3–5
9 Lindsay, S.L. *et al.* (2010) Olfactory mucosa for transplant-mediated repair: a complex tissue for a complex injury? *Glia* 58, 125–134
10 Niimura, Y. (2009) Evolutionary dynamics of olfactory receptor genes in chordates: interaction between environments and genomic contents. *Hum. Genomics* 4, 107–118

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

11 Verbeurgt, C. *et al.* (2014) Profiling of olfactory receptor gene expression in whole human olfactory mucosa. *PLoS ONE* 9, e96333
12 Damm, M. *et al.* (2004) Epidemiologie und Therapie von Riechstörungen in Deutschland Österreich und der Schweiz. *HNO* 52, 112–120
13 Mattes, R.D. *et al.* (1990) Dietary evaluation of patients with smell and/or taste disorders. *Am. J. Clin. Nutr.* 51, 233–240
14 Schredl, M. *et al.* (2009) Information processing during sleep: the effect of olfactory stimuli on dream content and dream emotions. *J. Sleep Res.* 18, 285–290
15 Lundstrom, J.N. *et al.* (2013) Maternal status regulates cortical responses to the body odor of newborns. *Front. Psychol.* 4, 597
16 Hummel, T. and Nordin, S. (2005) Olfactory disorders and their consequences for quality of life. *Acta Otolaryngol.* 125, 116–121
17 Rinaldi, A. (2007) The scent of life. The exquisite complexity of the sense of smell in animals and humans. *EMBO Rep.* 8, 629–633
18 Croy, I. *et al.* (2014) Olfactory disorders and quality of life: an updated review. *Chem. Senses* 39, 185–194
19 Deems, D.A. *et al.* (1991) Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch. Otolaryngol. Head Neck Surg.* 117, 519–528
20 Merkonidis, C. *et al.* (2015) Characteristics of chemosensory disorders: results from a survey. *Eur. Arch. Otorhinolaryngol.* 272, 1403–1416
21 Hummel, T. *et al.* (1997) 'Sniff' Sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chem. Senses* 22, 39–52
22 Doty, R.L. and Agrawal, U. (1989) The shelf life of the University of Pennsylvania Smell Identification Test (UPSIT). *Laryngoscope* 99, 402–404
23 Lapid, H. *et al.* (2011) Neural activity at the human olfactory epithelium reflects olfactory perception. *Nat. Neurosci.* 14, 1455–1461
24 Doty, R.L. *et al.* (1984) Smell identification ability: changes with age. *Science* 226, 1441–1443
25 Stevens, J.C. *et al.* (1989) Olfactory adaptation and recovery in old age. *Perception* 18, 265–276
26 Doty, R.L. *et al.* (1985) A cross-cultural study on sex differences in odor identification ability. *Neuropsychologia* 23, 667–672
27 Doty, R.L. and Cameron, E.L. (2009) Sex differences and reproductive hormone influences on human odor perception. *Physiol. Behav.* 97, 213–228
28 Hummel, T. and Welge-Luessen, A. (2006) Assessment of olfactory function. *Adv. Otorhinolaryngol.* 63, 84–98
29 Nakamura, H. *et al.* (1995) Olfactory disturbances caused by the anti-cancer drug tegafur. *Eur. Arch. Otorhinolaryngol.* 252, 48–52
30 Tsou, C.-C. and Chien, J.-Y. (2014) Olfactory disturbance related to pyrazinamide. *QJM* 107, 217–218
31 Grossman, S. (1953) Loss of taste and smell due to propylthiouracil therapy. *N. Y. State J. Med.* 53, 1236
32 Schiffman, S.S. and Zervakis, J. (2002) Taste and smell perception in the elderly: effect of medications and disease. *Adv. Food Nutr. Res.* 44, 247–346
33 Ackerman, B.H. and Kasbekar, N. (1997) Disturbances of taste and smell induced by drugs. *Pharmacotherapy* 17, 482–496
34 Konstantinidis, I. *et al.* (2009) Anosmia after general anaesthesia: a case report. *Anaesthesia* 64, 1367–1370
35 Lötsch, J. *et al.* (2001) Effects of the opioid remifentanil on olfactory function in healthy volunteers. *Life Sci.* 69, 2279–2285
36 Oertel, B.G. *et al.* (2015) Lack of fluconazole effects on human chemosensation. *Int. J. Clin. Pharmacol. Ther.* 53, 13–20
37 Lötsch, J. *et al.* (2015) Drug-target based cross-sectional analysis of olfactory drug effects. *Eur. J. Clin. Pharmacol.* 71, 461–471
38 Buck, L. and Axel, R. (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 65, 175–187
39 Gilad, Y. and Lancet, D. (2003) Population differences in the human functional olfactory repertoire. *Mol. Biol. Evol.* 20, 307–314
40 Jones, D.T. and Reed, R.R. (1989) Golf: an olfactory neuron specific-G protein involved in odorant signal transduction. *Science* 244, 790–795
41 Lötsch, J. *et al.* (2012) Sniffing out pharmacology: interactions of drugs with human olfaction. *Trends Pharmacol. Sci* 33, 193–199
42 Hálasz, N. and Shepherd, G.M. (1983) Neurochemistry of the vertebrate olfactory bulb. *Neuroscience* 10, 579–619
43 Ache, B.W. and Young, J.M. (2005) Olfaction: diverse species, conserved principles. *Neuron* 48, 417–430
44 Hu, P. *et al.* (2007) Computational prediction of cancer-gene function. *Nat. Rev. Cancer* 7, 23–34
45 Law, V. *et al.* (2014) DrugBank 4.0: shedding new light on drug metabolism. *Nucleic Acids Res.* 42, D1091–D1097
46 Huang, D.W. *et al.* (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat. Protoc.* 4, 44–57
47 Nai, Q. *et al.* (2010) Activation of alpha1 and alpha2 noradrenergic receptors exert opposing effects on excitability of main olfactory bulb granule cells. *Neuroscience* 169, 882–892
48 Zimnik, N.C. *et al.* (2013) α(1A)-Adrenergic regulation of inhibition in the olfactory bulb. *J. Physiol.* 591, 1631–1643
49 Araneda, R.C. and Firestein, S. (2006) Adrenergic enhancement of inhibitory transmission in the accessory olfactory bulb. *J. Neurosci.* 26, 3292–3298
50 Young, T.M. and Mathias, C.J. (2004) Taste and smell disturbance with the alpha-adrenoceptor agonist midodrine. *Ann. Pharmacother.* 38, 1868–1870
51 Lötsch, J. *et al.* (2014) Functional genomics suggest neurogenesis in the adult human olfactory bulb. *Brain Struct. Funct.* 219, 1991–2000
52 Fernandez-Irigoyen, J. *et al.* (2012) Proteomic atlas of the human olfactory bulb. *J. Proteomics* 75 (13), 4005–4016
53 Panagiotopoulos, G. *et al.* (2005) Decreasing nasal mucus Ca++ improves hyposmia. *Rhinology* 43, 130–134
54 Zelano, C. *et al.* (2007) Dissociated representations of irritation and valence in human primary olfactory cortex. *J. Neurophysiol.* 97, 1969–1976
55 Hawrylycz, M.J. *et al.* (2012) An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* 489, 391–399
56 Maresh, A. *et al.* (2008) Principles of glomerular organization in the human olfactory bulb: implications for odor processing. *PLoS ONE* 3, e2640
57 Ashburner, M. *et al.* (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat. Genet.* 25, 25–29
58 Camon, E. *et al.* (2004) The Gene Ontology Annotation (GOA) Database: sharing knowledge in Uniprot with Gene Ontology. *Nucleic Acids Res.* 32, D262–D266
59 Camon, E. *et al.* (2003) The Gene Ontology Annotation (GOA) project: implementation of GO in SWISS-PROT, TrEMBL, and InterPro. *Genome Res.* 13, 662–672
60 Ultsch, A. and Lötsch, J. (2014) Functional abstraction as a method to discover knowledge in gene ontologies. *PLoS ONE* 9, e90191
61 Carbon, S. *et al.* (2009) AmiGO: online access to ontology and annotation data. *Bioinformatics* 25, 288–289
62 Dugue, G.P. and Mainen, Z.F. (2009) How serotonin gates olfactory information flow. *Nat. Neurosci.* 12, 673–675
63 Mann, N.M. (2002) Management of smell and taste problems. *Cleve. Clin. J. Med.* 69, 329–336
64 Damm, M. *et al.* (2014) Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *Laryngoscope* 124, 826–831
65 Lötsch, J. and Geisslinger, G. (2010) Bedside-to-bench pharmacology: a complementary concept to translational pharmacology. *Clin. Pharmacol. Ther.* 87, 647–649
66 Landis, B.N. *et al.* (2010) Chemosensory interaction: acquired olfactory impairment is associated with decreased taste function. *J. Neurol.* 257, 1303–1308
67 Youngentob, S.L. and Kent, P.F. (1995) Enhancement of odorant-induced mucosal activity patterns in rats trained on an odorant. *Brain Res.* 670, 82–88
68 Hudson, R. and Distel, H. (1998) Induced peripheral sensitivity in the developing vertebrate olfactory system. *Ann. N. Y. Acad. Sci.* 855, 109–115
69 Wang, H.-W. *et al.* (1993) Induction of olfactory receptor sensitivity in mice. *Science* 260, 998–1000
70 Wang, L. *et al.* (2004) Evidence for peripheral plasticity in human odour response. *J. Physiol.* 554, 236–244
71 Henning, H. (1916) *Der Geruch*. Johann Ambrosius Barth
72 Livermore, A. and Laing, D.G. (1996) Influence of training and experience on the perception of multicomponent odor mixtures. *J. Exp. Psychol. Hum. Percept. Perform.* 22, 267–277
73 Cain, W.S. *et al.* (1995) Life-span development of odor identification, learning, and olfactory sensitivity. *Perception* 24, 1457–1472
74 Engen, T. and Bosack, T.N. (1969) Facilitation in olfactory detection. *J. Comp. Physiol. Psychol.* 68, 320–326
75 Venn, J. (1880) On the diagrammatic and mechanical representation of propositions and reasonings. *Dublin Philos. Mag. J. Sci.* 9, 1–18
76 Quint, C. *et al.* (2002) The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Otolaryngol.* 122, 877–881
77 Hummel, T. *et al.* (2002) Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. *Laryngoscope* 112, 2076–2080

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012

78 Gudziol, V. *et al.* (2007) Sildenafil affects olfactory function. *J. Urol.* 177, 258–261
79 Gudziol, V. and Hummel, T. (2009) Effects of pentoxifylline on olfactory sensitivity: a postmarketing surveillance study. *Archiv. Otolaryngol. Head Neck Surg.* 135, 291–295
80 Reden, J. *et al.* (2011) The effect of a herbal combination of primrose, gentian root, vervain, elder flowers, and sorrel on olfactory function in patients with a sinonasal olfactory dysfunction. *Rhinology* 49, 342–346
81 Reden, J. *et al.* (2011) Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope* 121, 679–682
82 Reden, J. *et al.* (2012) Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. *Laryngoscope* 122, 1906–1909
83 Walter, C. *et al.* (2014) Effects of 20 mg oral Delta-tetrahydrocannabinol on the olfactory function of healthy volunteers. *Br. J. Clin. Pharmacol.* 78, 961–969
84 Venn, J. (1880) On the diagrammatic and mechanical representation of propositions and reasonings. *Dublin Philos. Mag. J. Sci.* 9, 1–18

Please cite this article in press as: Lötsch, J. et al. Olfactory drug effects approached from human-derived data, Drug Discov Today (2015), http://dx.doi.org/10.1016/j.drudis.2015.06.012