PERSPECTIVES

OPINION

Drugs, their targets and the nature and number of drug targets

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Abstract | What is a drug target? And how many such targets are there? Here, we consider the nature of drug targets, and by classifying known drug substances on the basis of the discussed principles we provide an estimation of the total number of current drug targets.

Estimations of the total number of drug targets are presently dominated by analyses of the human genome, which are limited for various reasons, including the inability to infer the existence of splice variants or interactions between the encoded proteins from gene sequences alone, and the fact that the function of most of the DNA in the genome remains unclear. In 1997, when 100,000 protein-coding sequences were hypothesized to exist in the human genome, Drews and Ryser estimated the number of molecular targets 'hit' by all marketed drug substances to be only 482 (REF. 1). In 2002, after the sequencing of the human genome, others arrived at ~8,000 targets of pharmacological interest, of which nearly 5,000 could be potentially hit by traditional drug substances, nearly 2,400 by antibodies and ~800 by protein pharmaceuticals[2]. And on the basis of ligand-binding studies, 399 molecular targets were identified belonging to 130 protein families, and ~3,000 targets for small-molecule drugs were predicted to exist by extrapolations from the number of currently identified such targets in the human genome[3].

In summary, current target counts are of the order of 10^2, whereas estimations of the number of potential drug targets are an order of magnitude higher. In this paper, we consider the nature of drug targets, and use a classification based on this consideration, and a list of approved drug substances (TABLES 1–8, BOX 1), to estimate the number of known drug targets, in the following categories:

- Enzymes (TABLE 1)
- Substrates, metabolites and proteins (TABLE 2)
- Receptors (TABLE 3)
- Ion channels (TABLE 4)
- Transport proteins (TABLE 5)
- DNA/RNA and the ribosome (TABLE 6)
- Targets of monoclonal antibodies (TABLE 7)
- Various physicochemical mechanisms (TABLE 8)
- Unknown mechanism of action (BOX 1)

The nature of drug targets

A prerequisite for counting the number of targets is defining what a target is. Indeed, this is the crucial, most difficult and also most arbitrary part of the present approach. For the purpose of this paper, we consider a target to be a molecular structure (chemically definable by at least a molecular mass) that will undergo a specific interaction with chemicals that we call drugs because they are administered to treat or diagnose a disease. The interaction has a connection with the clinical effect(s).

This definition implies several constraints. First, the medicinal goal excludes pharmacological and biochemical tools from the present approach. Second, a major constraint is a lack of technique. Life, including disease, is dynamic, but as we do not yet directly observe the interactions of drugs and targets, and only partly notice the subsequent biochemical 'ripples' they produce; we are generally limited to 'still life' (for example, X-ray crystal structures)

and to treating targets as static objects. In the case of G-protein-coupled receptors (GPCRs), the pharmaceutically most useful class of receptors, a re-organization of the protein after drug binding was derived from biochemical data[4], but such approaches are still in their infancy.

For most drugs, several if not many targets were identified. Consequently, we had to decide for every drug substance or drug class which target(s) to include in our list. For this, we relied on the existence of literature data that showed some connection between the interaction of the drug with the biochemical structure of the target and the clinical effect(s) (not side effects). A chemical with a certain reactivity or binding property is used as a drug because of its clinical effects, but it should be stressed that it can be challenging to prove that a certain molecular interaction is indeed the one triggering the effect(s). In this respect, knockout mice are proving increasingly useful. For example, a lack of effect of a drug in mice lacking a particular target can provide strong support that the effects of the drug are mediated by that target (for a review on knockout mice in target validation, see REF. 5).

We therefore considered the construction of knockout animals that lack the target, with pertinent observation of effects, strong proof or disproof for a certain mechanism of action. In the case of receptors, we regarded the availability and testing of both agonists and antagonists (and/or inverse agonists) proof for a mechanism. In the case of enzyme inhibitors (for example, cyclooxygenase inhibitors), molecular interactions and effects of structurally unrelated substances that are largely identical were considered proof of the mechanism. In cases where a drug interaction on the biochemical level was found, but the biochemical pathway was not yet known to be connected with the observed drug effect, the target was not counted. For antipsychotic drugs in particular, a plethora of target receptors and receptor subtypes are known and discussed (see PDSP K_i Database in Further information and BOX 2). However, extensive discussion of such issues is outside the scope of an article

Table 1a | **Enzymes**

Type	Activity of drug	Drug examples
Oxidoreductases		
Aldehyde dehydrogenase	Inhibitor	Disulfiram[39]
Monoamine oxidases (MAOs)	MAO-A inhibitor	Tranylcypromine[40], moclobemide[41]
	MAO-B inhibitor	Tranylcypromine[40]
Cyclooxygenases (COXs)	COX1 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[42,43]
	COX2 inhibitor	Acetylsalicylic acid, profens, acetaminophen and dipyrone (as arachidonylamides)[44]
Vitamin K epoxide reductase	Inhibitor	Warfarin, phenprocoumon[45]
Aromatase	Inhibitor	Exemestane[46]
Lanosterol demethylase (fungal)	Inhibitor	Azole antifungals[47]
Lipoxygenases	Inhibitor	Mesalazine[48]
	5-lipoxygenase inhibitor	Zileuton[49]
Thyroidal peroxidase	Inhibitor	Thiouracils[50]
Iodothyronine-5′ deiodinase	Inhibitor	Propylthiouracil[50]
Inosine monophosphate dehydrogenase	Inhibitor	Mycophenolate mofetil[51]
HMG-CoA reductase	Inhibitor	Statins[52]
5α-Testosterone reductase	Inhibitor	Finasteride, dutasteride[53]
Dihydrofolate reductase (bacterial)	Inhibitor	Trimethoprim[54]
Dihydrofolate reductase (human)	Inhibitor	Methotrexate, pemetrexed[55]
Dihydrofolate reductase (parasitic)	Inhibitor	Proguanil[56]
Dihydroorotate reductase	Inhibitor	Leflunomide[57]
Enoyl reductase (mycobacterial)	Inhibitor	Isoniazid[58]
Squalene epoxidase (fungal)	Inhibitor	Terbinafin[59]
Δ14 reductase (fungal)	Inhibitor	Amorolfin[60]
Xanthine oxidase	Inhibitor	Allopurinol[61]
4-Hydroxyphenylpyruvate dioxygenase	Inhibitor	Nitisinone[62]
Ribonucleoside diphosphate reductase	Inhibitor	Hydroxycarbamide[63]
Transferases		
Protein kinase C	Inhibitor	Miltefosine[64,65]
Bacterial peptidyl transferase	Inhibitor	Chloramphenicol[67]
Catecholamine-O-methyltransferase	Inhibitor	Entacapone[68]
RNA polymerase (bacterial)	Inhibitor	Ansamycins[69]
Reverse transcriptases (viral)	Competitive inhibitors	Zidovudine[70,71]
	Allosteric inhibitors	Efavirenz[72,73]
DNA polymerases	Inhibitor	Acyclovir, suramin[74,75]
GABA transaminase	Inhibitor	Valproic acid[76], vigabatrin[77]
Tyrosine kinases	PDGFR/ABL/KIT inhibitor	Imatinib[78]
	EGFR inhibitor	Erlotinib[79]
	VEGFR2/PDGFRβ/KIT/FLT3	Sunitinib[66]
	VEGFR2/PDGFRβ/RAF	Sorafenib[109]
Glycinamide ribonucleotide formyl transferase	Inhibitor	Pemetrexed[55]
Phosphoenolpyruvate transferase (MurA, bacterial)	Inhibitor	Fosfomycin[80,81]
Human cytosolic branched-chain aminotransferase (hBCATc)	Inhibitor	Gabapentin[82]

EGFR, epidermal growth factor receptor; GABA, γ-amino butyric acid; HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

Table 1b | **Enzymes**

Type	Activity of drug	Drug examples
Hydrolases (proteases)		
Aspartyl proteases (viral)	HIV protease inhibitor	Saquinavir, indinavir[94]
Hydrolases (serine proteases)		
Unspecific	Unspecific inhibitors	Aprotinine[95]
Bacterial serine protease	Direct inhibitor	β-lactams[96]
Bacterial serine protease	Indirect inhibitor	Glycopeptides[97]
Bacterial lactamases	Direct inhibitor	Sulbactam[98]
Human antithrombin	Activator	Heparins[99-101]
Human plasminogen	Activator	Streptokinase[102,103]
Human coagulation factor	Activator	Factor IX complex, Factor VIII[104]
Human factor Xa	Inhibitor	Fondaparinux[105]
Hydrolases (metalloproteases)		
Human ACE	Inhibitor	Captopril[106]
Human HRD	Inhibitor	Cilastatin[107]
Human carboxypeptidase A (Zn)	Inhibitor	Penicillamine[108]
Human enkephalinase	Inhibitor	Racecadotril[110]
Hydrolases (other)		
26S proteasome	Inhibitor	Bortezomib[83]
Esterases	AChE inhibitor	Physostigmine[84]
	AChE reactivators	Obidoxime[85]
	PDE inhibitor	Caffeine[86]
	PDE3 inhibitor	Amrinon, milrinone[87]
	PDE4 inhibitor	Papaverine[88]
	PDE5 inhibitor	Sildenafil[89]
	HDAC inhibitor	Valproic acid[76]
	HDAC3/HDAC7 inhibitor	Carbamezepine[90]
Glycosidases (viral)	α-glycosidase inhibitor	Zanamivir, oseltamivir[91]
Glycosidases (human)	α-glycosidase inhibitor	Acarbose[92]
Lipases	Gastrointestinal lipases inhibitor	Orlistat[93]
Phosphatases	Calcineurin inhibitor	Cyclosporin[111]
	Inositol polyphosphate phosphatase inhibitor	Lithium ions[112,113]
GTPases	Rac1 inhibitor	6-Thio-GTP (azathioprine metabolite)[114]
Phosphorylases	Bacterial C55-lipid phosphate dephosphorylase inhibitor	Bacitracin[115]
Lyases		
DOPA decarboxylase	Inhibitor	Carbidopa[116]
Carbonic anhydrase	Inhibitor	Acetazolamide[117]
Histidine decarboxylase	Inhibitor	Tritoqualine[118]
Ornithine decarboxylase	Inhibitor	Eflornithine[119]
Soluble guanylyl cyclase	Activator	Nitric acid esters, molsidomine[120-123]
Isomerases		
Alanine racemase	Inhibitor	D-Cycloserine[124]
DNA gyrases (bacterial)	Inhibitor	Fluoroquinolones[125]
Topoisomerases	Topoisomerase I inhibitor	Irinotecan[126]
	Topoisomerase II inhibitor	Etoposide[127]
Δ8,7 isomerase (fungal)	Inhibitor	Amorolfin[128]
Ligases (also known as synthases)		
Dihydropteroate synthase	Inhibitor	Sulphonamides[129]
Thymidylate synthase (fungal and human)	Inhibitor	Fluorouracil[130]
Thymidylate synthase (human)	Inhibitor	Methotrexate, pemetrexed[55,131]
Phosphofructokinase	Inhibitor	Antimony compounds[132]
mTOR	Inhibitor	Rapamycin[133]
Haem polymerase (*Plasmodium*)	Inhibitor	Quinoline antimalarials[134]
1,3-β-D-glucansynthase (fungi)	Inhibitor	Caspofungin[135]
Glucosylceramide synthase	Inhibitor	Miglustat[136]

ACE, angiotensin-converting enzyme; AChE, acetylcholinesterase; HDAC, histone deacetylase; HRD, human renal dehydropeptidase; mTOR, mammalian target of rapamycin; PDE, phosphodiesterase.

Table 2 | **Substrates, metabolites and proteins**

Substrate	Drug substance
Asparagine	Asparaginase[137]
Urate	Rasburicase (a urate oxidase)[138]
VAMP–synaptobrevin, SNAP25, Syntaxin	Light chain of the botulinum neurotoxin (Zn-endopeptidase)[139]

SNAP, synaptosomal-associated protein; VAMP, vesicle-associated membrane protein.

that tries to cover 'all' drug substances. For the present purpose, we chose to limit our analysis to published consensus data on one to three of the main biochemical targets of drug substances. If there was no consensus or proof of target and/or target–effect connection, we included the respective substances in a part of our list called 'Unknown mechanism of action'.

The dynamics of drug effects. It would ultimately be desirable to move away from a static target definition, but this is hindered mainly by our inability to gauge the interaction of the aforementioned 'ripples' — in other words, the actual pharmacodynamics of drugs. All drugs somehow interfere with signal transduction, receptor signalling and biochemical equilibria. For many drugs we know, and for most we suspect, that they interact with more than one target. So, there will be simultaneous changes in several biochemical signals, and there will be feedback reactions of the pathways disturbed. In most cases, the net result will not be linearly deducible from single effects. For drug combinations, this is even more complicated. A mechanism-based simulation of pharmacodynamic drug–drug interactions was published recently[6], highlighting the complexity of interaction analyses for biological systems. Awareness is also increasing of the nonlinear correlation of molecular interactions and clinical effects. For example, the importance of receptor–receptor interactions (receptor mosaics) was recently summarized for GPCRs, resulting in the hypothesis that cooperativity is important for the decoding of signals, including drug signals[7]. Another paper reported dopamine fluctuations after

administration of cocaine, followed by a gradual increase in steady-state dopamine concentration[8]. Indeed, the dynamics of the response are what really matters, but are difficult to assess experimentally. Further examples of dynamic (process) mechanisms of drug action include non-covalent modifications of the active centre (for example, acetylation of bacterial transpeptidases by β-lactam antibiotics); allosteric modulation (for example, benzodiazepine modulation of GABA (γ-amino butyric acid) receptors); drugs that require the receptor to be in a certain state for binding and inhibition (for example, 'trapping' of K^+ channels by methanesulphoanilide anti-arrhythmic agents[9]); drugs that exert their effect indirectly and require a functional background (for example, the catechol-*O*-methyl transferase inhibitor entacapone, the effect of which is due to the accumulation of non-metabolized dopamine); anti-infectives that require the target organism to be in an active, growing state (for example β-lactams); molecules requiring activation (prodrugs, such as paracetamol); and cases of modifications of a substrate or cofactor (for example, asparaginase, which depletes tumour cells of asparagine; isoniazide, which is activated by mycobacteria leading to an inactive covalently modified NADH; and vancomycin, which binds to the building block bacteria use for constructing their cell wall).

The macro- and micro-world of targets. So, for estimations of the total number of targets, a clinically relevant 'target' might consist not of a single biochemical entity, but the simultaneous interference of a number of receptors (pathways, enzymes and so on).

Only this will give a net clinical effect that might be considered beneficial. As yet, we are unable to count 'targets' in this sense ('macro-targets'), and it is only by chance that most of the current *in vitro* screening techniques will identify drugs that work through such targets.

Greater knowledge of how drugs interact with the body (mechanisms of action, drug–target interactions) has led to a reduction of established drug doses and inspired the development of newer, highly specific drug substances with a known mechanism of action. However, a preoccupation with the molecular details has sometimes resulted in a tendency to focus only on this one aspect of the drug effects. For example, cumulative evidence now suggests that the proven influence of certain psychopharmaceuticals on neurotransmitter metabolism has little to do with the treatment of schizophrenia or the effectiveness of the drug for this indication[10]. Here, we touch on a very basic and important point that cannot be expanded in the context of this paper but which deserves to be stressed: with all our efforts to understand the molecular basis of drug action, we must not fall into the trap of reductionism. As Roald Hoffmann aptly said in his speech at the Nobel Banquet:

"Chemistry reduced to its simplest terms, is not physics. Medicine is not chemistry .... knowledge of the specific physiological and eventually molecular sequence of events does not help us understand what [a] poet has to say to us."

With diseases such as type 1 diabetes, for example, the molecule insulin is indeed all that is needed to produce a cure, although we cannot imitate its regulated secretion. With diseases such as psychoses, for example, antipsychotic drugs might not correct nor even interfere with the aspect of the human constitution that is actually deranged, and with such drugs molecular determinism might be counterproductive to the use and development of therapeutic approaches. It is thought that rather than chemically providing a 'cure', these drugs make the patient more responsive to a therapy that acts at a different level. Reflections on molecular targets are very important because drugs are molecules, but it is important not to be too simplistic.

Returning to the key question, what do we count as a target? In the search for molecular reaction partners of drug substances, we will have to be content with losing sight

Box 1 | **Drugs with unknown mechanism of action**

4-Aminosalicylic acid | Alendronate | Ambroxol | Arsenic trioxide | Becaplermin | Bexarotene | Chloral hydrate | Clofazimine | Dactinomycin (RNA synthesis inhibitor) | Dapsone (folic acid synthesis inhibitor) | Diethyl carbamazine | Diethyl ether | Diloxanide | Dinitric oxide | Ethambutol | Gentian violet | Ginkgolides | Griseofulvin | Halofantrine | Halothane | Hydrazinophthalazine | Limefantrine (antimalarial; prevents haem polymerization) | Levetiracetam | Mebendazole | Methyl-(5-amino-4-oxopentanoate) | Niclosamide | Pentamidine | Podophyllotoxin | Procarbazine | Selenium sulphide

Box 2 | **One drug — many targets**

Over the past 20 years, drug approval authorities and many pharmacologists have moved away from combination therapies and asked for rational, single-drug, single-target therapies. This is understandable, as it rapidly becomes challenging to analyse the contributions of multiple drugs or those that hit multiple targets to the observed effects, both desirable and undesirable. The principle that blocking a single pharmacological target with high potency is desirable because it minimizes the side effects that come with non-specific drugs has become well-established, almost dogma, in drug development circles. However, a few examples will suffice to show that it is an oversimplification. First, despite the appeal of a single-drug-target strategy for drug development, the most effective anti-arrhythmic compound, amiodarone, is the 'dirtiest' of all anti-arrhythmics[33]. Second, the problems with highly selective cyclooxygenase-2-inhibitors are considered to be due to their very selectivity, which seems to tip the balance of pro- and anti-thrombotic mediators in an unfavourable way[34]. Third, propranolol is the first and classic β-sympatholytic agent, but it has neither an absolute selectivity for an adrenoceptor subtype nor does it address receptors exclusively; for example, it also inhibits phosphatidic acid phosphorylase. It is not clear whether the latter activity contributes to the net clinical effects (hypotension and so on)[35]. Fourth, oestrogens not only have an intracellular nuclear receptor, but also activate a membrane-bound one as well (GPR30)[36]. The effects of oestrogen result from the interplay of the two mechanisms. Fifth, for papaverine, a smooth-muscle relaxant agent, the following activities were recorded, and all seem to be important for the net effect: cyclic nucleotide phosphodiesterase inhibition, Ca^{2+}-channel blockade and α-adrenoreceptor antagonism[37]. And last, the anticancer drug imatinib was originally moved into clinical development on the basis of its capacity to inhibit a single target: the BCR–ABL kinase. It has since become clear that its success could be linked to interaction with at least two other targets; indeed, two anticancer drugs, sorafenib and sunitinib, that were developed to inhibit multiple kinases have recently been approved. As with antipyschotics[30], such 'dirty' or 'promiscuous' anticancer drugs might be increasingly sought in the near future[38].

of some of the net biochemical and especially clinical effects of the drug's action. A target definition derived from the net effect rather than the direct chemical interaction will require input from systems biology, a nascent research field that promises to significantly affect the drug discovery process[11]. At the other end of the scale of precision, we can define some targets very precisely on the molecular level: for example, we can say that dihydropyridines block the $Ca_V1.2a$ splicing variant in heart muscle cells of L-type high-voltage activated calcium channels. This is an example of a 'micro-target'. It does make sense to define it because a subtype or even splicing variant selectivity could alter the effectiveness of calcium channel blockers. We could further differentiate between genetic, transcriptional, post-transcriptional or age differences between individuals, and again this will make sense in some cases. But for a target count, a line needs to be drawn somewhere, otherwise the number of individual patients that receive a drug could be counted and equated with the number of known targets. In summary, we will count neither macro- nor micro-targets, but something in between — admittedly a somewhat arbitrary distinction.

Classification of current drugs
There are a number of possible ways to classify drug substances (active pharmaceutical ingredients). From the end of the

nine-teenth century until the 1970s, drug substances were classified in the same way as other chemical entities: by the nature of their primary elements, functional moieties or organic substance class. Recently, the idea of classifying drug substances strictly according to their chemical constitution or structure has been revived. Numerous databases now attempt to gather and organize information on existing or potential drug substances according to their chemical structure and diversity. The objective is to create substance 'libraries' that contain pertinent information about possible ligands for new targets (for example, an enzyme or receptor) of clinical interest[12,13] and, more importantly, to understand the systematics of molecular recognition[14,15] (ligand–receptor).

> ❝ In situations in which the dynamic actions of the drug substance stimulate, or inhibit, a biological process, it is necessary to move away from the descriptions of single proteins, receptors and so on and to view the entire signal chain as the target. ❞

At present, the most commonly used classification system for drug substances is the ATC system[16] (see WHO Collaborating Centre for Drug Statistics Methodology, Further information). It categorizes drug substances at different levels: *a*natomy, *t*herapeutic properties and *c*hemical properties. We recently proposed an alternative classification system[17], although we did not follow it fully in the arrangement of entries in TABLES 1–8, BOX 1, as explained below.

Classification of drug substances according to targets. In TABLES 1–8, we arranged drug substances according to their mechanism of action. Although the term 'mechanism of action' itself implies a classification according to the dynamics of drug substance effects at the molecular level, the dynamics of these interactions are only speculative models at present, and so mechanism of action can currently only be used to describe static (micro)targets, as discussed above.

The actual depth of detail used to define the target is primarily dependent on the amount of knowledge available about the target and its interactions with a drug. If the target structure has already been determined, it could still be that the molecular effect of the drug cannot be fully described by the interactions with one target protein alone. For example, anti-bacterial oxazolidinones interact with 23S-rRNA, tRNA and two polypeptides, ultimately leading to inhibition of protein synthesis. In this case, a description of the mechanism of action that only includes interactions with the 23S-rRNA target would be too narrowly defined. In particular, in situations in which the dynamic actions of the drug substance stimulate, or inhibit, a biological process, it is necessary to move away from the descriptions of single proteins, receptors and so on and to view the entire signal chain as the target. Indeed, it has been pointed out by Swinney in an article on this topic that "two components are important to the mechanism of action ... The first component is the initial mass-action-dependent interaction ... The second component requires a coupled biochemical event to create a transition away from mass-action equilibrium" and "drug mechanisms that create transitions to a non-equilibrium state will be more efficient"[18]. This consideration again stresses that dynamics are essential for effective drug action and, as discussed above, indicates that an effective drug target comprises a biochemical system rather than a single molecule.

Table 3a | **Receptors**

Type	Activity of drug	Drug examples
Direct ligand-gated ion channel receptors		
GABA$_A$ receptors	Barbiturate binding site agonists	Barbiturate[140]
	Benzodiazepine binding site agonists	Benzodiazepines[141]
	Benzodiazepine binding site antagonists	Flumazenil[142]
Acetylcholine receptors	Nicotinic receptor agonists	Pyrantel (of *Angiostrongylus*), levamisole[143,144]
	Nicotinic receptor stabilizing antagonists	Alcuronium[145]
	Nicotinic receptor depolarizing antagonists	Suxamethonium[146]
	Nicotinic receptor allosteric modulators	Galantamine[147]
Glutamate receptors (ionotropic)	NMDA subtype antagonists	Memantine[148]
	NMDA subtype expression modulators	Acamprosate[149]
	NMDA subtype phencyclidine binding site antagonists	Ketamine[150]
G-protein-coupled receptors		
Acetylcholine receptors	Muscarinic receptor agonists	Pilocarpine[151]
	Muscarinic receptor antagonists	Tropane derivatives[152,153]
	Muscarinic receptor M$_3$ antagonists	Darifenacine[154]
Adenosine receptors	Agonists	Adenosine[155]
	Adenosine A$_1$ receptor agonists	Lignans from valerian[156]
	Adenosine A$_1$ receptor antagonists	Caffeine, theophylline
	Adenosine A$_{2A}$ receptor antagonists	Caffeine, theophylline[157]
Adrenoceptors[158,159]	Agonists	Adrenaline, noradrenaline, ephedrine
	α_1- and α_2-receptors agonists	Xylometazoline
	α_1-receptor antagonists	Ergotamine[160]
	α_2-receptor, central agonists	Methyldopa (as methylnoradrenaline)
	β-adrenoceptor antagonists	Isoprenaline
	β_1-receptor antagonists	Propranolol, atenolol
	β_2-receptor agonists	Salbutamol
	β_2-receptor antagonists	Propranolol
Angiotensin receptors	AT$_1$-receptors antagonists	Sartans[161]
Calcium-sensing receptor	Agonists	Strontium ions[162]
	Allosteric activators	Cinacalcet[163]
Cannabinoid receptors	CB$_1$- and CB$_2$-receptors agonists	Dronabinol[164]
Cysteinyl-leukotriene receptors	Antagonists	Montelukast[165]
Dopamine receptors[166]	Dopamine receptor subtype direct agonists	Dopamine, levodopa
	D$_2$, D$_3$ and D$_4$ agonists	Apomorphine
	D$_2$, D$_3$ and D$_4$ antagonists	Chlorpromazine, fluphenazine, haloperidol, metoclopramide, ziprasidone
Endothelin receptors (ET$_A$, ET$_B$)	Antagonists	Bosentan[167]
GABA$_B$ receptors	Agonists	Baclofen[168]
Glucagon receptors	Agonists	Glucagon[169]
Glucagon-like peptide-1 receptor	Agonists	Exenatide[170]
Histamine receptors	H$_1$-antagonists	Diphenhydramine[171]
	H$_2$-antagonists	Cimetidine[172]
Opioid receptors[173,174]	μ-opioid agonists	Morphine, buprenorphine
	μ-, κ- and δ-opioid antagonists	Naltrexone
	κ-opioid antagonists	Buprenorphine
Neurokinin receptors	NK$_1$ receptor antagonists	Aprepitant[175]

GABA, γ-amino butyric acid; NMDA, *N*-methyl-D-aspartate.

Table 3b | **Receptors**

Type	Activity of drug	Drug examples
Prostanoid receptors	Agonists	Misoprostol, sulprostone, iloprost[176]
Prostamide receptors	Agonists	Bimatoprost[177]
Purinergic receptors	P_2Y_{12} antagonists	Clopidogrel[178]
Serotonin receptors	Subtype-specific (partial) agonists	Ergometrine, ergotamine[160]
	5-HT_{1A} partial agonists	Buspirone[179]
	$5\text{-HT}_{1B/1D}$ agonists	Triptans[180]
	5-HT_{2A} antagonists	Quetiapine, ziprasidone[181]
	5-HT_3 antagonists	Granisetron[182]
	5-HT_4 partial agonists	Tegaserode[183]
Vasopressin receptors[184]	Agonists	Vasopressin
	V_1 agonists	Terlipressin[185]
	V_2 agonists	Desmopressin
	OT agonists	Oxytocin
	OT antagonists	Atosiban
Cytokine receptors		
Class I cytokine receptors	Growth hormone receptor antagonists	Pegvisomant[186]
	Erythropoietin receptor agonists	Erythropoietin[187]
	Granulocyte colony stimulating factor agonists	Filgrastim[188]
	Granulocyte-macrophage colony stimulating factor agonists	Molgramostim[189]
	Interleukin-1 receptor antagonists	Anakinra[190]
	Interleukin-2 receptor agonists	Aldesleukin[191]
TNFα receptors	Mimetics (soluble)	Etanercept[192]
Integrin receptors		
Glycoprotein IIb/IIIa receptor	Antagonists	Tirofiban[193]
Receptors associated with a tyrosine kinase		
Insulin receptor	Direct agonists	Insulin[194]
Insulin receptor	Sensitizers	Biguanides[195]
Nuclear receptors (steroid hormone receptors)		
Mineralocorticoid receptor[196]	Agonists	Aldosterone
	Antagonists	Spironolactone
Glucocorticoid receptor	Agonists	Glucocorticoids[197]
Progesterone receptor	Agonists	Gestagens[198]
Oestrogen receptor[199]	Agonists	Oestrogens
	(Partial) antagonists	Clomifene
	Antagonists	Fulvestrant
	Modulators	Tamoxifen, raloxifene[200]
Androgen receptor[201,202]	Agonists	Testosterone[203]
	Antagonists	Cyproterone acetate[204]
Vitamin D receptor[205,206]	Agonists	Retinoids[207]
ACTH receptor agonists	Agonists	Tetracosactide (also known as cosyntropin)[208]
Nuclear receptors (other)		
Retinoic acid receptors	RARα agonists	Isotretinoin[209]
	RARβ agonists	Adapalene, isotretinoin[210]
	RARγ agonists	Adapalene, isotretinoin[210]
Peroxisome proliferator-activated receptor (PPAR)	PPARα agonists	Fibrates[211,212]
	PPARγ agonists	Glitazones[213]
Thyroid hormone receptors	Agonists	L-Thyroxine[214]

ACTH, adrenocorticotropic hormone.

Table 4 | **Ion channels**

Type	Activity of drug	Drug examples
Voltage-gated Ca²⁺ channels		
General	Inhibitor	Oxcarbazepine[216]
In *Schistosoma sp.*	Inhibitor	Praziquantel[217]
L-type channels	Inhibitor	Dihydropyridines, diltiazem, lercanidipine, pregabalin, verapamil[218–223]
T-type channels	Inhibitor	Succinimides[224]
K⁺ channels[225]		
Epithelial K⁺ channels	Opener Inhibitor	Diazoxide, minoxidil[226,227] Nateglinide, sulphonylureas[228,229]
Voltage-gated K⁺ channels	Inhibitor	Amiodarone[230]
Na⁺ channels		
Epithelial Na⁺ channels (ENaC)[231]	Inhibitor	Amiloride, bupivacaine, lidocaine, procainamide, quinidine
Voltage-gated Na⁺ channels	Inhibitor	Carbamazepine, flecainide, lamotrigine, phenytoin, propafenone, topiramate, valproic acid[232–239]
Ryanodine-inositol 1,4,5-triphosphate receptor Ca²⁺ channel (RIR-CaC) family		
Ryanodine receptors	Inhibitor	Dantrolene[240,241]
Transient receptor potential Ca²⁺ channel (TRP-CC) family		
TRPV1 receptors	Inhibitor	Acetaminophen (as arachidonylamide)[242]
Cl⁻ channels[243]		
Cl⁻ channel	Inhibitor (mast cells) Opener (parasites)	Cromolyn sodium[244] Ivermectin[245]

TRPV, transient receptor potential vanilloid.

A further criterion needed for the full categorization of drug substances according to their target is the anatomical localization of the target. This is essential for a differentiation between substances with the same biochemical target, but a different organ specificity (for example, nifedipine and verapamil are both L-type calcium channel inhibitors; the former interacts primarily with vascular calcium channels and the latter with cardiac calcium channels). However, in the tables, we chose not to include this criterion as it would have made the list more cumbersome.

Categorization of current drugs. We began by sorting substances according to their target, considering the following biochemical structures to be target families: enzymes (TABLE 1); substrates, metabolites and proteins (TABLE 2); receptors (TABLE 3); ion channels (TABLE 4); transport proteins (TABLE 5); DNA/RNA and the ribosome (TABLE 6); targets of monoclonal antibodies (TABLE 7); various physicochemical mechanisms (TABLE 8); and unknown mechanism of action (BOX 1).

Within the families, individual enzymes, receptors and so on were included if they were identified in the literature as the main target(s) of an approved drug substance. We filled the list shown in TABLES 1–8, BOX 1 by including the following drugs and their corresponding main targets: all substances included in the thirteenth *Model List of Essential Medicines* published by the World Health Organization[19] (excluding the categories: vitamins, minerals, oxygen as a narcotic gas, and diagnostics); drug substances included in the FDA's *Approved Drug Products* list (25th edition, 2005)[20]; all newly developed drugs from the past 5 years introduced on the German market[21]; and drugs approved by the FDA in 2004 with a new mechanism of action, again excluding substitution therapeuticals[22]. We checked the resulting list against the lists of targets in Drews and Ryser's paper[1], a list of enzyme targets in the supplemental material to Robertson's paper[23], and a compilation of receptors produced for nomenclature purposes[24], and we further supplemented our list using the current edition of Mutschler's German textbook *Drug Actions*[25].

In this way, TABLES 1–8, BOX 1 include only those targets relevant for the effect of drugs currently on the market. For drug substances or classes in the lists, selected references are given that are concerned with the mechanism of action; the references are arranged by target family and subfamily, and within the subfamilies, alphabetically. New targets and mechanisms of action were not listed if a corresponding drug that interacts with the target has not yet been marketed. Drugs currently undergoing clinical trials have been excluded for the sake of briefness and also because of the numerous status fluctuations of such drugs.

Table 5 | **Transport proteins (uniporters, symporters and antiporters)**

Type[246]	Activity of drug	Drug examples
Cation-chloride cotransporter (CCC) family[247]	Thiazide-sensitive NaCl symporter, human inhibitor	Thiazide diuretics[248]
	Bumetanide-sensitive NaCl/KCl symporters, human inhibitor	Furosemide[249]
Na⁺/H⁺ antiporters	Inhibitor	Amiloride, triamterene[250–252]
Proton pumps	Ca²⁺-dependent ATPase (PfATP6; Plasmodia) inhibitor	Artemisinin and derivatives[253]
	H⁺/K⁺-ATPase inhibitor	Omeprazole[254]
Na⁺/K⁺ ATPase	Inhibitor	Cardiac glycosides[255]
Eukaryotic (putative) sterol transporter (EST) family	Niemann-Pick C1 like 1 (NPC1L1) protein inhibitor	Ezetimibe[256]
Neurotransmitter/Na⁺ symporter (NSS) family[257,258]	Serotonin/Na⁺ symporter inhibitor	Cocaine, tricyclic antidepressants, paroxetine[257–260]
	Noradrenaline/Na⁺ symporter inhibitor	Bupropion, venlafaxine[261,262]
	Dopamine/Na⁺ symporter inhibitor	Tricyclic antidepressants, cocaine, amphetamines[257,258]
	Vesicular monoamine transporter inhibitor	Reserpine[263,264]

Table 6 | **DNA/RNA and the ribosome**

Target	Activity of drug	Example drugs
Nucleic acids		
DNA and RNA[265]	Alkylation	Chlorambucil, cyclophosphamide, dacarbazine[266–268]
	Complexation	Cisplatin[269,270]
	Intercalation	Doxorubicin[271]
	Oxidative degradation	Bleomycin[272]
	Strand breaks	Nitroimidazoles[273]
RNA	Interaction with 16S-rRNA	Aminoglycoside antiinfectives[274]
	Interaction with 23S-rRNA	Macrolide antiinfectives[275]
	23S-rRNA/tRNA/2-polypeptide complex	Oxazolidinone antiinfectives[276]
Spindle	Inhibition of development	Vinca alkaloids[277]
	Inhibition of desaggregation	Taxanes[278]
Inhibition of mitosis	—	Colchicine[279]
Ribosome[280]		
30S subunit (bacterial)	Inhibitors	Tetracyclines[281]
50S subunit (bacterial)	Inhibitors	Lincosamides, quinupristin–dalfopristin[282, 283]

It should be noted that for a certain target, we did not include all drug substances that address it, but just a representative example of the structural classes in use. In some cases, such as the β-lactams, we cited the structural class instead of individual representatives. We tried to name the first substance of a class, if it is still marketed.

A subdivision of the major groups according to the 'anatomy' (cell type or physiological functional unit within which the target is located and acted on by the drug) and the substance class has been carried out in just a few cases for which the literature seemed to be unanimous about the identification and relevance of such a subdivision. In order to keep TABLES 1–8, BOX 1 readable, the main focus has been given to the classification of the substance according to its biochemical target.

A categorization going into further detail is outside the scope of this article, although of course obtaining further molecular and cellular detail is possible in some cases. For example, transport proteins have been subclassified in great detail[26,27], and target lists have been produced for cancer drugs[28]. An extensive list of affinities of CNS drugs for vast numbers of targets is also available online at the PDSP Database (see Further information). The latter list illustrates well the point discussed previously: that in many cases it will not help to know a single target, because the clinical effect is caused by patterns of target interactions.

Of course, our list is an approximation. And a categorization of compounds according to their mechanism of action will inevitably lead to a group of remaining drugs with proven clinical effectiveness, but an unknown molecular target. Such compounds can, if at all, only hypothetically be classified within the selected major groups. The ATC classification system, with its systematic categorization according to therapeutic aspects (for example, 'analgesics') does not have this problem, as every substance in the list shows

— or is claimed to show — a therapeutic effect. It will also be the case that, as with the ATC system, certain drug substances appear more than once in the list. Indeed, it will happen more often than in the ATC system, owing to the fact that some drug effects are based on the synergistic effects of more than one mechanism of action.

The number of drug targets
At the level of target definition we chose, which is illustrated by the table rows, we counted 218 targets. The most prominent target families included hydrolases in the enzyme family, GPCRs in the receptor family and voltage-gated Ca^{2+} channels in the ion-channel family. The usefulness of a target family in this count is probably a consequence of its commonness, the format of assays (with recent binding-affinity based assays having contributed little as yet), and the nature of the diseases that affect the developed world.

A large part of this paper is concerned with the nature of drug targets and the need to consider the dynamics of the drug–targets (plural intended) interactions, as these considerations were used to define what we would eventually count. Many successful drugs have emerged from the simplistic 'one drug, one target, one disease' approach that continues to dominate pharmaceutical thinking, and we have generally used this approach when counting targets here. However, there is an increasing readiness to challenge this paradigm[29–32]. We have discussed its constraints and limitations in light of the emerging network view of

Table 7 | **Targets of monoclonal antibodies**

Target	Agent
Vascular endothelial growth factor	Bevacizumab[284,285]
Lymphocyte function-associated antigen 1	Efalizumab[286]
Epidermal growth factor receptor	Cetuximab[284,287]
Human epidermal growth factor receptor 2	Trastuzumab[288]
Immunoglobulin E (IgE)	Omalizumab[289]
CD-3	Muromonab-CD3[290]
CD-20	Rituximab, ibritumomab tiuxetan, ^{131}I-tositumomab[291,292]
CD-33	Gemtuzumab[293]
CD-52	Alemtuzumab[294]
F protein of RSV subtypes A and B	Palivizumab[295]
CD-25	Basiliximab, daclizumab[296,297]
Tumour-necrosis factor-α	Adalimumab, infliximab[298,299]
Glycoprotein IIb/IIIa receptor	Abciximab[300]
α4-Integrin subunit	Natalizumab[301]

Table 8 | **Various physicochemical mechanisms**

Mechanism	Agent
Ion exchange	Fluoride
Acid binding	Magnesium hydroxide, aluminium hydroxide
Adsorptive	Charcoal, colestyramine
Adstringent	Bismuth compounds
Surface-active	Simeticone, chlorhexidine, chloroxylene
Surface-active on cell membranes	Coal tar
Surface-active from fungi	Nystatin, amphotericin B
Mucosal irritation	Anthrones, anthraquinones
Osmotically active	Lactulose, dextran 70, polygeline, glucose, electrolyte solutions, mannitol
Water binding	Urea, ethanol
UV absorbant	4-Aminobenzoic acid derivatives
Reflective	Zinc oxide, titanium dioxide
Oxidative	Tannines, polyphenoles, dithranol, polyvidon iodide, silver nitrate, hypochlorite, permanganate, benzoylperoxide, nitroimidazoles, nitrofuranes, temoporfin (mainly via singlet oxygen, cytostatic drug), verteporfin (mainly via singlet oxygen, ophthalmic drug)
Reduce disulphide bridges	D-Penicillamine, N-acetyl-cysteine
Complexing agents	Al^{3+}, arsenic compounds
Salt formation	Sevelamer
Modification of tertiary structure	Enfuvirtide (from HIV glycoprotein 41)

targets. The recent progress made in our understanding of biochemical pathways and their interaction with drugs is impressive. However, it may be that 'the more you know, the harder it gets'. It is not the final number of targets we counted that is the most important aspect of this Perspective; rather, we stress how considerations about what to count can help us gauge the scope and limitations of our understanding of the molecular reaction partners of active pharmaceutical ingredients. Targets are highly sophisticated, delicate regulatory pathways and feedback loops but, at present, we are still mainly designing drugs that can single out and, as we tellingly say, 'hit' certain biochemical units — the simple definable, identifiable targets as described here. This is not as much as we might have hoped for, but in keeping with the saying of one of the earliest medical practitioners, Hippocrates: "Life is short, and art long; the crisis fleeting; experience perilous, and decision difficult." Humility remains important in medical and pharmaceutical sciences and practice.

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FURTHER INFORMATION
PDSP K_i Database: http://kidb.case.edu
Therapeutic Target Database:
http://xin.cz3.nus.edu.sg/group/cjttd/ttd.asp
WHO Collaborating Centre for Drug Statistics Methodology:
http://www.whocc.no/atcddd/
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