Section 1
General Concept for Target-based Safety Assessment

Antitargets and Drug Safety, First Edition. Edited by László Urbán, Vinod F. Patel, and Roy J. Vaz.

1
Side Effects of Marketed Drugs: The Utility and Pitfalls of Pharmacovigilance

Steven Whitebread, Mateusz Maciejewski, Alexander Fekete, Eugen Lounkine, and László Urbán

1.1
Introduction

Drug discovery projects can learn a lot from existing drugs, for instance, how well they perform in a particular indication and patient population, but also which side effects they cause. While efficacies for a particular indication may be quite similar between compounds, their side effect profiles may vary considerably. Many diseases are managed by drugs acting at various targets and diverse chemical structures might be available for the same target. Incidence of adverse drug reactions (ADRs) could vary for drugs acting at the same target due to different off-target profiles and different levels of required exposure of parent and metabolites. These are strongly dependent on the pharmacological interaction with the target (e.g., potency and binding kinetics [1]) and availability in different organs (e.g., blood–brain barrier penetration and high concentrations in the gastrointestinal system or liver).

One can differentiate between ADRs associated with on- and off-targets and we recognize that on-target-related side effects could also vary by exposure in a particular organ (e.g., presence or absence of brain access of H1 antihistamines [2]) or the mode of interaction with the therapeutic target (e.g., inhibition, full or partial agonism, and allosteric modulation [3]). One can learn a considerable lesson from on-target-related side effects and apply this knowledge when the same target emerges as an off-target with a different drug in a different indication [4]. In this respect, monoclonal antibodies (mAbs) can provide excellent opportunities for the study of on-target ADRs due to their high target specificity. mAbs for various kinase targets in oncology indications highlighted pathways that were involved in various physiological functions in addition to pathways associated with cancer [5].

To unequivocally identify off-targets for clinical ADRs is not an easy matter. Common symptoms such as headache, chest pain, or cough could

Antitargets and Drug Safety, First Edition. Edited by László Urbán, Vinod F. Patel, and Roy J. Vaz.

be associated with several targets or not associated with any, just developing as concomitant symptoms during treatment with a drug. However, when the same side effect is observed with drugs for different indications or with diverse structural features, a common off-target can be suspected. These clinical observations do not always manifest during clinical trials, either because their incidence is low and linked to a particular patient subpopulation [6] or because the development of the side effect takes a long period of time [7]. Until recently, there was little knowledge of the underlying mechanisms of most ADRs, and they were often denoted as "idiosyncratic" adverse reactions. The vast majority of hepatic and cardiac side effects fall into this nebulous category. Recent increase in off-target and pathway profiling has opened the door to the understanding of many side effects [8–10]. The concept is very simple: drugs or any new molecular entity (NME) can be tested in assays representing targets that are closely associated with clinical side effects [8]. This method was applied to marketed drugs and environmental chemicals/toxins in various formats and recently applied to over 8000 compounds in the frame of a federal collaboration called "Toxicity Testing in the 21st Century" (Tox21), comprised of EPA, the National Institute of Environmental Health Sciences/National Toxicology Program, National Center for Advancing Translational Sciences, and the Food and Drug Administration. Data from this orchestrated effort is being released to the public as the collection of ToxCast.[1)]

In vitro safety pharmacology profiling has opened the door to the identification of target–ADR pairs by common target–side effect linkage to different drugs, based on the principle described above. The data obtained from these studies revealed unknown off-targets and, in a significant number of drugs, pharmacological promiscuity. Importantly, it helped to develop *in silico* models [11] that extended the scope of ADR prediction during drug discovery beyond the capabilities of *in vitro* profiling. The integration of the experimental and *in silico* approaches flourish within the concept of the reductionist chemistry approach to drug discovery [12]. The new, large-scale capability of predictive safety profiling demands uniform ontology, which could be used broadly with clarity for various models and supports translation of preclinical findings into clinical ADRs. Today, the MedDRA (Medical Dictionary for Regulatory Activities) terms are broadly used for ADR annotation of targets and conveniently link their function to system organ classes with the benefit of clinical interpretation. Table 1.1 demonstrates this concept on a selected set of CNS targets, highlighting the diverse effects of agonists and antagonists. In this chapter, we will apply the above-described approach to marketed drugs to demonstrate its powerful translational capabilities, including applications for drug design, competitive intelligence, and possible drug repositioning.

1) ToxCast, http://epa.gov/ncct/toxcast/data.html.

Table 1.1 Selected CNS receptors potentially involved in psychoactive effects.

CNS receptor	Associated neurological/psychoactive effects (selection)	
	Agonism	**Antagonism**
5-HT_{1A}	Nervousness, agitation, miosis, hypothermia, cardiovascular regulation (hypotension and bradycardia)	May contribute to depression and suicidal ideation
5-HT_{2A}	Behavioral effects, smooth muscle contraction, hallucination	No relevant CNS side effects known
5-HT_7	May alter circadian rhythm, psychiatric disorders/schizophrenia might be a concern	No relevant CNS side effects known
CB1	Alteration of cognition and memory, sleep disturbance, drowsiness, sedation, locomotor dysfunction, bronchodilation, cardiovascular regulation (hypotension and bradycardia)	Emesis, depression, suicidal tendencies; the inverse agonist rimonabant may cause suicidal ideation
D_1	May induce dyskinesia, extreme arousal, flushing, nausea, vomiting, dizziness, locomotor activation	Tremor; depression, anxiety, and suicidal intent were observed with D_1 and D_5 antagonists; hypertension
D_{2L}	Drowsiness, dizziness, and nausea especially with the first dose and some psychosis may occur after long-term treatment; vasodilatation, ↓ heart rate; ↓ pituitary hormone secretions (e.g., prolactin)	Tardive dyskinesia (impairment of voluntary movement), akathisia (an inability to sit still or remain motionless), and other extrapyramidal effects (Parkinson-like syndrome)
D_3	Cognitive and emotional functions, psychosis, neurodegeneration, coordination, substance abuse, sedation, schizophrenia; it may induce hair loss (see pramipexole)	Dyskinesia (impairment of voluntary movement), akathisia (an inability to sit still or remain motionless), and other extrapyramidal effects (Parkinson-like syndrome)
D_5	No relevant CNS side effects known	Suicidal intent (observed with D_1 and D_5 antagonists)
GABA-A	Major receptor involved in inhibitory neurotransmission: psychological, neurological, sensory functions, sedation, movement disturbances, hallucinations, and potentially leading to tolerance	Mimics the symptoms of epilepsy, potential anxiogenics, and proconvulsants
GABA-A benzodiazepine	Somnolence, suppression of REM sleep or dreaming, impaired motor function, impaired coordination, impaired balance, dizziness, depression, anterograde amnesia (especially pronounced in higher doses), withdrawal and abuse risks	May cause seizures (strong black box warning)

(*continued*)

Table 1.1 (*Continued*)

CNS receptor	Associated neurological/psychoactive effects (selection)	
	Agonism	**Antagonism**
NMDA	Glycine site: may reduce negative and improve cognitive function in schizophrenics, cause seizures, neurotoxicity	PCP site: anesthetic properties, may induce psychosis (schizophrenia-like), hallucination, delirium and disoriented behavior, may cause seizures, neurotoxicity, ligands of the PCP receptor induce symptoms in humans that are virtually indistinguishable from schizophrenia; polyamine site: polyamine system is linked to suicidal ideation
OpD	Analgesia, sedation, physical dependence, emotional behavior, decrease of GI motility	No relevant CNS side effects known
OpK	Analgesia, sedation, hypotension, tachycardia, diuresis, dysphoria, dizziness, paresthesia and antipruritic effects (TRK-820), interaction with dopaminergic transmission, hallucination; full or partial agonists produce psychotomimetic effects, in the case of the mixed (partial) agonist/antagonist analgesic drugs (e.g., butorphanol, nalbuphine, pentazocine) the psychotomimesis is undesirable and serves to limit abuse potential	Selective kappa opioid antagonists explored for their effects in the treatment of a wide variety of areas including cocaine addiction, depression, and feeding behavior, and have been proposed as a treatment for psychosis and schizophrenia
OpM	Analgesia, sedation, physical dependence, bowel dysfunction, constipation, respiratory depression, modulation of cough reflex, development of tolerance and addiction risks	Selective peripheral antagonists are used to treat postoperative ileus and to reverse the effects of opioid agonists (e.g., naloxone, naltrexone, and nalmefene), may cause diarrhea

Adapted from Ref. [8].
CB1: cannabinoid 1; $D_{1,2L,3,5}$: dopamine 1, 2 (long form), 3, 5; GABA-A: gamma-aminobutyric acid A; NMDA: *N*-methyl aspartate; OpD, -K, -M: opioid delta, kappa, mu; PCP: phencyclidine; $5\text{-}HT_{1A,2A,7}$: serotonin 1A, 2A, 7.

1.2 Postmarketing Pharmacovigilance

ADRs (or their absence) are major contributors to the well-being of patients, compliance, and medical expenses [13–16]. They are mostly discovered during clinical trials; however, the full scope and impact of ADRs can be

determined only by postmarketing monitoring and surveillance (e.g., FDA Adverse Event Reporting System (FAERS) [17]). FAERS is a public database containing reports on adverse drug reactions and medication errors submitted to the FDA. It is designed to align with the international safety reporting guidance issued by the International Conference on Harmonization (ICH) E2B(R3). The database contains over 4.6 million entries and is updated on a quarterly basis. The database provides ADRs associated with a particular drug with rich patient information, including age, gender, reason for hospitalization/doctor's visit, medication, and outcome. Although it gives information on the dosage, it lacks pharmacokinetic (PK) data; thus, determination of exposure and, more importantly, therapeutic index in a particular case is not possible. This is rectified by complex searchable databases such as the FDA, API, and Thomson-Reuters' Integrity or PharmaPendium,[2] an online information repository that reviews drug safety issues by providing access to integrated preclinical, clinical, and postmarketing adverse effects together with PK data. Figure 1.1b is a screenshot from the FAERS profile of panitumumab (Vectibix) in PharmaPendium. The reported side effects are listed by preclinical and postmarketing appearance. As Vectibix affects a single protein kinase target, epidermal growth factor receptor (EGFR, HER1), it is presumed that all observed side effects are associated with this single target [18]. As expected, EGFR inhibitors would affect epidermal integrity and health (see Chapter 15); therefore, it is not surprising that panitumumab carries a box warning[3] for severe dermatitis, clearly recorded by FAERS. The association of skin lesions with EGFR inhibition is further confirmed with all marketed small-molecule EGFR inhibitors (Figure 1.1a). Armed with this information, one can deselect small-molecule kinase inhibitors that carry EGFR as an off-target. Thus, this approach (termed reverse translation) is used to identify target–ADR associations and it is applied to the drug discovery process for early mitigation of off-target effects that would be a safety risk in the clinic [19].

As kinase inhibitors are relatively new in the clinic, their side effect profiles are relatively less well known. Pharmacovigilance is therefore of major importance to determine their ADR profiles and drug labeling (Table 1.2). The clinical introduction of monoclonal antibodies for kinase targets made it possible to link ADRs with well-defined therapeutic targets as these antibodies provide selectivity, which is a rare feature of small-molecule kinase inhibitors.

While FAERS is by far not perfect, it can provide a rich source of postmarketing information and supports identification of ADRs undetected during clinical trials. PharmaPendium[2] gives access to the FAERS database and

2) http://thomsonreuters.com/integrity/; http://www.elsevier.com/online-tools/promo-page/pharmapendium/pbt_pp_adwordsgeneric_jan2014/home.

3) Vectibix, www.vectibix.com/.

(a)

ErbB1 (EGRF, HER1)

Viewing by area affected
View by name

	Preclinical Data view all 574	Clinical Data view all 3541	Post-Marketing Reports (AERS) view all 31788
Blood and lymphatic system disorders	24	139	3720
Cardiac disorders	4	118	2270
Skin and subcutaneous tissue disorders	60	609	7557
Vascular disorders	3	91	2765

(b)

Panitumumab

Adverse Effects / Toxicity :

Viewing by area affected
View by name

	Preclinical Data view all 112	Clinical Data view all 867	Post-Marketing Reports (AERS) view all 5252
Blood and lymphatic system disorders	1	14	809
Cardiac disorders	1	13	283
Congenital, familial and genetic disorders	1	no data	18
Ear and labyrinth disorders	no data	1	15
Endocrine disorders	1	no data	4
Eye disorders	3	47	168
Gastrointestinal disorders	6	132	1700
General disorders and administration site conditions	5	96	1357
Hepatobiliary disorders	1	12	158
Immune system disorders	no data	24	102
Infections and infestations	2	62	1255
Investigations	36	41	715
Metabolism and nutrition disorders	15	93	1111
Musculoskeletal and connective tissue disorders	no data	11	198
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	3	530
Nervous system disorders	3	21	508
Pregnancy, puerperium and perinatal conditions	5	no data	no data
Psychiatric disorders	1	8	113
Renal and urinary disorders	1	4	284
Reproductive system and breast disorders	6	no data	28
Respiratory, thoracic and mediastinal disorders	1	69	963
Skin and subcutaneous tissue disorders	22	191	1515
Vascular disorders	no data	25	453

Figure 1.1 FAERS representation of side effects of epidermal growth factor receptor (EGFR, HER1, ErbB1) inhibitors. (a) Enhanced skin and subcutaneous ADR representation of marketed EGFR inhibitors (cetuximab, lapatinib ditosylate, and panitumumab) (not all ADRs shown). (b) FAERS profile of panitumumab (Vectibix) represents the typical high occurrence of skin and GI lesions associated with the inhibition of the therapeutic target. (Courtesy of PharmaPendium.)

allows the search for PK information that is essential to determine the therapeutic index for drugs [20]. The most reliable source of information on ADRs is obtained from drug labels, and the FDA ensures they are updated regularly.

Table 1.2 Kinases involved in cardiovascular risks: clinical evidence based on monoclonal antibody treatment.

Kinase target	Human safety (information based on FDA label)	Animal toxicity	Animal genetics – KO (OMIM)
ErbB2 (HER2)	Trastuzumab: black box for cardiomyopathy (supported by multi-KI lapatinib: warning for decrease in LVEF)	Trastuzumab: no cardiac toxicity in mice/monkeys; no TCR in adult monkey and human cardiac myocytes	Severe dilated cardiomyopathy, decreased contractility
EGFR (HER1)	Cetuximab: black box for cardiopulmonary arrest and/or sudden death (multi-KI erlotinib: warning for myocardial infarction/ischemia)	Cetuximab: no cardiac toxicity in mice/monkeys EKB-569 and AG-1478: significant changes in left ventricular wall thickness and cardiac function	Aortic valve disease and aortic stenosis
VEGFR2 (KDR)	Bevacizumab (anti-VEGF-A): warning for arterial thromboembolic events (ATEs) and hypertension (supported by multi-KI sunitinib: warning for cardiac toxicity/decrease in LVEF; supported by multi-KI sorafenib: warning for cardiac ischemia/infarction and hypertension)	Bevacizumab: no cardiac toxicity seen preclinically	Lack of VEGF(R)-deficient mouse models due to lethality
PDGFRa	Possibility for contributory factor for cardiac ADRs associated with certain KIs (current label data for dasatinib, sunitinib, and sorafenib); PDGFRs are expressed in cardiomyocytes	Depending on kinase spectrum	

Note that preclinical safety pharmacology evaluation did not signal cardiac toxicity; however, genetic evidence supported the observed side effects.

1.3 Polypharmacy and Pharmacological Promiscuity of Marketed Drugs

Marketed drugs are optimized molecules with two major requirements to be fulfilled: therapeutic efficacy and acceptable safety window at the prescribed dose [20]. Drug design can focus on a single molecular target or on a pathway with a defined phenotypic readout of the therapeutic effect. Most drugs belong to the first group, even when a combination of targets might be preferable for a therapeutic effect (e.g., for congestive heart failure). Remarkably "clean" compound profiles could be found with antihypertensive, cholesterol-lowering drugs, bisphosphonates, and several other groups of medicines (see Table 1.3 for antihypertensive drugs). In general, drugs for broad applications for non-life-threatening diseases should have a clean sheet of off-targets, particularly as they

Table 1.3 Lack of pharmacological promiscuity of antihypertensive drugs.

Drug	Off-targets found
Adrenergic receptor antagonists	
Alpha blockers	
Bunazosin	hERG
Prazosin	μ-Opioid
Terazosin	μ-Opioid
Beta blockers	
Atenolol	—
Propranolol	5-HT receptor family
Ca channel blockers	
Dihydropyridines	
Nifedipine	Adenosine receptors
Nitrendipine	PXR
ACE inhibitors	
Captopril	H1
Enalapril	—
Cilazapril	—
Angiotensin II receptor antagonists	
Candesartan	—
Losartan	PDE3
Irbesartan	PDE3

are often used in conjunction with other drugs for a different disease in the same patient population. According to the Center for Disease Control (CDC) statistics, about 37% of the over 60-year-old population use more than five prescription drugs [21]. Considering drug–drug interactions, possible cumulative effects of on- and off-targets, the most commonly used drugs in this patient population such as the above-mentioned cholesterol-lowering and antihypertensive drugs should be as safe as possible. As an example, patients who are taking a particular drug for hypertension might also need medication for psychiatric indications, such as depression. Many of the psychotropic agents have effects at adrenergic receptors that will have an additional effect on blood pressure [22] and might cause orthostatic hypotension, a serious issue in the elderly [23,24].

When exploring marketed databases, two classes of drugs, cancer treatments and antipsychotics, generally have a trend to be more promiscuous [25,26]. At present, the majority of small-molecule cancer drugs aim for inhibition of the highly conserved ATP binding site in the kinase family. Thus, binding to this site is likely to produce drugs with low selectivity between kinase targets and occasionally to non-kinase targets as well (see Figure 1.2).

Kinase inhibitors are new to clinical practice; thus, pharmacovigilance is of major importance to determine their long-term side effect profiles and provide information for correct drug labeling. As mentioned earlier, mAbs, but also the more specific allosteric kinase inhibitors, can give the best characterization of ADRs associated with a specific kinase target (as an example, Table 1.2 shows

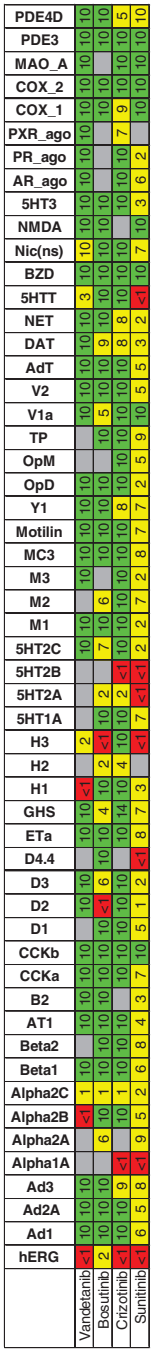

Figure 1.2 Non-kinase target-related promiscuity of selected kinase inhibitors vandetanib, bosutinib, crizotinib, and sunitinib. The non-kinase-related pharmacological promiscuity of the kinase inhibitors varies broadly and does not reflect on their kinase selectivity. Note that sunitinib (Sutent) is an extremely promiscuous kinase inhibitor. Red: $IC_{50} < 1$ μM; yellow: $IC_{50} = 1–10$ μM; green: $IC_{50} \geq 10$ μM.

the drug labels of some mAb kinase inhibitors). A new generation of kinase inhibitors offers less promiscuity as they do not target the ATP binding pocket, but aim for allosteric modulator sites, for example, Akt inhibitors [27].

The other particularly promiscuous group of drugs is the family of antipsychotics [28]. We took several of the most commonly used antidepressants and annotated their on- and off-target hits (Figure 1.3). Adenosine, adrenergic, dopamine, histamine, serotonergic, muscarinic receptors, and neurotransmitter transporters DAT, NET, and SERT are those targets that are often encountered with these drugs. While it is considered that a combination of targets could be responsible for the antidepressant therapeutic effects, it is obvious that they could also exhibit psychiatric ADRs. For example, all SSRIs are labeled for suicidal intent and behavior in pediatric use [29] (see Chapter 20).

Specific off-target effects within a particular indication may strongly depend on the similarity between chemical structures of drugs associated with different therapeutic targets. As an example, we examined antihypertensive adrenergic receptor blockers, Ca channel blockers, angiotensin inhibitors, and ACE inhibitors (Table 1.3). Most of these drugs show high specificity of binding to the therapeutic target with the angiotensin II receptor blockers showing particularly good selectivity. None of these compounds carry any serious safety-related warnings. We investigated the side effect profile of the angiotensin receptor antagonist FAERS profiles and will use this example to highlight some shortcomings of the adverse reaction reporting systems. While the most common reported effects of angiotensin receptor inhibition include hypotension, dry mouth, excessive thirst, dizziness, and slow or irregular heartbeat, there are no major ADRs that would warrant warnings. However, the compiled ADR profile of these drugs (Figure 1.4) shows a large number of entries with particular emphasis on cardiovascular events. Over 16% of the entries are concerned with cardiac side effects, 18% of the reports are associated with vascular disorders, almost half of the "investigations" reported are related to cardiac and vascular effects, and finally 29% of nervous system disorders are CNS vascular events. This list of major ADRs suggests that this group of drugs or their metabolites seriously affect the cardiovascular system and generate safety issues. However, none of the drugs or their metabolites is promiscuous, and considering the major indications for these drugs (hypertension and congestive heart failure), we can attribute the above-mentioned cardiovascular events as symptoms of the treated diseases themselves, and with the exception of orthostatic hypotension and its consequences, others are not real ADRs. Thus, reports on adverse drug reactions are often biased by the disease the treatment is applied to and carry over many of the original symptoms. While this is a lesser issue during clinical trials, once released onto the market drugs lack the controlled environment of clinical trials; thus, the confidence in the reported ADRs is significantly diminished. This seems to be a general issue with the postmarketing reporting systems and should be taken into account by any pharmacovigilance analysis.

In the case of telmisartan, the observed cardiac disorders during clinical trials were about 7% of all registered ADRs, whereas FAERS reported 14%. One can argue that this can be due to the different, possibly more diverse and

DrugName	TradeName	Drug Class	THR	Ad1	Ad2A	Ad3	Alpha1A	Alpha2A	Alpha2B	Alpha2C	Beta1	Beta2	AT1	B2	CB1	CCKa	CCKb	D1
Risperidone	Risperdal	AAP	21	10	10	10	<1	1	<1	<1	10		10	10	10	10	10	<1
Olanzapine	Zyprexa	AAP	25	10	10	10	<1	4	1	<1	10	10	10	10	10	10	10	<1
Aripiprazole	Abilify	AAP	27	10	10	10	3	3	2	<1	<1	<1	10	10	10	10	10	
Trazodone	Desyrel	SARI	19	10	10	10	<1	<1	3	<1	10	10	10	10	10	10	10	10
Venlafaxine	Effexor	SNRI	9	10	10	10	10	10	10	10	10	10	10	10	5	10	10	
Duloxetine	Cymbalta	SNRI	20	10	10	10	1	10	4	1	10		10	10	10	10	10	
Citalopram	Celexa	SSRI	14	10	10	10	1	10	10	10	10	10	10	10	10	10	10	7
Sertraline	Zoloft	SSRI	16	10	10	10	1	10	3	3	10	10	10	10	10	10	10	
Fluoxetine	Prozac	SSRI	17	10	10	10	5	10	4	10	10	10	10	10	3	10	10	10
Paroxetine	Paxil	SSRI	22	10	10	10	2	10	10	8	10	10	10	10	3	10	10	10
Amitriptyline	Elavil	TCA	30	10	10	10	<1	3	<1	<1	10	10	1	10	10	10	10	<1
Nortriptyline	Sensoval	TCA	38	10	10	10	<1	9	<1	<1	10	5	10	10	10	10	10	<1

DrugName	D2	D3	D4.4	ETa	GHS	H1	H2	H3	5HT1A	5HT2A	5HT2B	5HT2C	M1	M2	M3	MC3	Motilin	Y1	OpD	OpK	OpM
Risperidone	<1	<1	<1	10	10	<1	<1	10	1	<1	<1	<1	10	10		10	10	10	10	10	10
Olanzapine	<1	<1	<1	10	10	<1	<1	10	4	<1	<1	<1	<1	<1	<1	10	10	10	10	10	10
Aripiprazole	<1	<1		10	10	<1		10			<1	1	10	10	10	10	10	10	10	10	
Trazodone	3	2	1	10	10	1	10	10	<1	<1	<1	1	10	10	10	10	10	10	10	10	10
Venlafaxine	10	10			10	1		7	10	<1	10	10	10	10	10	10	10	10	10	10	10
Duloxetine	7	5			10	9		10		<1	10	10	10	10	10	10	5	10	10	2	10
Citalopram	10	2	10	10	10	2	<1	10	10	2	<1	4	10	8	10	10	10	10	10	10	10
Sertraline	10	10		10	10	10		10	10		9	5	10	10	10	7	10	10	10	<1	
Fluoxetine	8	10	10	10	10	6	2	10	10	<1	6	<1	10	10	4	10	10	10	10	2	10
Paroxetine	10	10	10	10	10	10	4	10	10	4	10	10	2	1	<1	10	10	10	<1	1	2
Amitriptyline	<1	<1	<1	10	10	<1	<1	10	4	<1	<1	<1	<1	<1	<1	10	10	10	10	1	10
Nortriptyline	6	<1		10	10	<1		10	8	<1	<1	<1	<1	<1	<1	10	10	10	10	<1	

DrugName	TP	V1a	V2	AdT	DAT	NET	5HTT	hERG	Ca2(L)	Ca2(N)	BZD	GABA A	Nic(ns)	NMDA	5HT3	AR	ERa	ERb	GR	PR	PXR	COX1	COX2	MAO A	PDE3	PDE4D
Risperidone	10	10	10	10	10	10	10	2	10	10	10		10	10	10	10	10	10	10	10		10	10	10	10	10
Olanzapine	10	10	10	10	10	10	10	11	10	10	10	10		10	2	10	10	10	10	10		10	7	10	10	10
Aripiprazole	10	10	10	10	4	8	<1	<1	10		10	10	10	10	10		10		10		10	10	10	10	2	10
Trazodone	10	10	10	10	10	10	<1	3	10	10	10	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Venlafaxine		10	10	10	10	10	<1	10	10	10	10	10	10	10	10	10	10		10	10	10	10	10	10	10	10
Duloxetine	10	10	10	10	1	<1	<1	2	10		10	10	10	10	10	10	10		10	10	10	10	10	10	10	10
Citalopram	10	10	10	10	10	6	<1	3	10	10	10	10		10	10	10	10	10	10	10		10	10	10	10	10
Sertraline	10	10	10	10	<1	5	<1	2	10		10	10	10	10	10		10		10		10	10	10	10	10	10
Fluoxetine	10	10	10	10	10	2	<1	5	10	10	10	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Paroxetine	10	10	10	10	1	<1	<1	3	2	10	10	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Amitriptyline	10	10	10	10	10	<1	<1	3	10	10	10	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10
Nortriptyline	10	10	10	10	3	<1	<1	3	10		10	10	10	10	10		10		10		10	10	10	10	10	8

Figure 1.3 The heat map demonstrates the high promiscuity of a group of frequently used antidepressants. SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; SNRI: serotonin–norepinephrine reuptake inhibitor; SARI: serotonin antagonist and reuptake inhibitor; AAP: atypical antipsychotic. Red: $IC_{50} < 1\ \mu M$; yellow: $IC_{50} = 1–10\ \mu M$; green: $IC_{50} \geq 10\ \mu M$; THR = target hit rate, the percentage of targets with an IC_{50} of $<10\ \mu M$ (not all targets are shown).

Viewing by area affected View by name	Preclinical Data view all 577	Clinical Data view all 2994	Post-Marketing Reports (AERS) view all 30750
Blood and lymphatic system disorders	16	55	1547
Cardiac disorders	31	138	5008
Congenital, familial and genetic disorders	18	3	284
Ear and labyrinth disorders	no data	27	529
Endocrine disorders	15	no data	268
Eye disorders	3	26	1369
Gastrointestinal disorders	66	324	4277
General disorders and administration site conditions	19	240	9294
Hepatobiliary disorders	20	43	1440
Immune system disorders	no data	20	606
Infections and infestations	1	420	2705
Investigations	165	407	8175
Metabolism and nutrition disorders	65	104	3863
Musculoskeletal and connective tissue disorders	no data	171	3613
Mutagenicity	3	no data	no data
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	6	1681
Nervous system disorders	21	362	7868
Pregnancy, puerperium and perinatal conditions	27	4	473
Psychiatric disorders	7	77	2176
Renal and urinary disorders	78	99	3694
Reproductive system and breast disorders	7	5	366
Respiratory, thoracic and mediastinal disorders	6	184	4268
Skin and subcutaneous tissue disorders	3	168	3321
Vascular disorders	no data	111	5585

Figure 1.4 A combined profile comprising representatives from the class of angiotensin II AT_1 receptor antagonists obtained from the FDA Adverse Event Reporting System. The case of angiotensin II antagonists demonstrates that reports on adverse drug reactions are often biased by the original symptoms of the disease the treatment is applied to. (Courtesy of PharmaPendium.)

significantly larger patient population. However, the same is true for vascular disorders, with 5% versus 12%, and for nervous system disorders, 7% compared with 24% of all reports. Accordingly, the label for telmisartan does not carry any warning for major cardiovascular adverse reactions, but correctly points to the possibility of orthostatic hypotension [30].

Drugs that are combinations of different active ingredients also cause a problem in the determination of target–ADR links. For example, local allergy medications have a combination of fexofenadine HCl and pseudoephedrine HCl [31]. This situation also occurs when several drugs are taken concomitantly and in FAERS only one is noted as the "suspect" drug. Thus, care should be taken of drug combinations when FAERS data are interpreted for target-related ADRs.

Finally, drugs withdrawn from the market provide valuable data for the reverse translation process. Drug withdrawals are based on the development of ADRs in the clinical setting that are life-threatening, cause unacceptable burden, or are difficult to manage [32]. The example we take is fenfluramine, an anorexiant that affects the serotonin transporter. Patients treated with fenfluramine developed cardiac valve disorders, a serious irreversible heart condition. FAERS

registered 19,141 reports with 59% of the reports associated with cardiac disorders, an extraordinarily high incidence. When further investigated, 38% of the observed cardiac disorders revealed various cardiac valve anomalies (data from PharmaPendium).[4] Based on this observation, fenfluramine was withdrawn from the market and the otherwise rare ADR was later linked to the agonist effect of the major metabolite, norfenfluramine, at the 5-HT_{2B} receptor [33].

While this book highlights targets that we consider "antitargets" under various conditions, in this chapter we focus on information gathering (data mining) that would support claims for target–ADR links. We highlighted the importance of using clinical data for reverse translation to identify the targets that are associated with side effects and we use this information to set up predictive assays for hazard identification during the early phases of the drug discovery process. We demonstrated the importance of this method in the process of parallel optimization for therapeutic effects and mitigation of adverse reactions. Targets incorporated into the *in vitro* pharmacological profiling process are annotated with information obtained from clinical ADRs, which enables the cost-effective prediction of side effects of chemical structural classes or single molecules in the preclinical setting.

On the other hand, we have to be cautious with data interpretation from clinical observations. Cases from FAERS demonstrate the pitfalls that can be encountered if a statistical analysis of the data is conducted without taking into account important factors such as the patient population and their medical condition, other administered drugs, and off-label use of drugs. We demonstrated with the case of antihypertensive drugs that symptoms characteristic for a particular disease could mask the true ADR profile of a drug and we need to keep this in perspective by relying more on the ADRs reported from phase 3 clinical trials. However, be aware of the small chance of ADRs developing very slowly during chronic treatment, which would not be seen in the trials, or of rare alleles in the broad random patient population.

References

1 Kenakin, T. and Christopoulos, A. (2013) Signalling bias in new drug discovery: detection, quantification and therapeutic impact. *Nature Reviews. Drug Discovery*, **12**, 205–216.

2 Kalpaklioglu, F. and Baccioglu, A. (2012) Efficacy and safety of H1-antihistamines: an update. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, **11**, 230–237.

3 Kenakin, T.P. (2012) Biased signalling and allosteric machines: new vistas and challenges for drug discovery. *British Journal of Pharmacology*, **165**, 1659–1669.

4 Majure, D.T., Greco, T., Greco, M., Ponschab, M., Biondi-Zoccai, G., Zangrillo, A., and Landoni, G. (2013) Meta-analysis of randomized trials of effect of milrinone on mortality in cardiac surgery: an update. *Journal of*

4) PharmaPendium, www.pharmapendium.com/drugs.do;jsessionid=6874369FAAE8591CDA98D076CCC4AAA5#browse=1&lookup=1&hierarchical=1&type=d&name=Fenfluramine&alpha=al_9&query=fenfluramine.

Cardiothoracic and Vascular Anesthesia, **27**, 220–229.

5 Bair, S.M., Choueiri, T.K., and Moslehi, J. (2013) Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives. *Trends in Cardiovascular Medicine*, **23**, 104–113.

6 Ortega, V.E., Hawkins, G.A., Moore, W.C., Hastie, A.T., Ampleford, E.J., Busse, W.W., Castro, M., Chardon, D., Erzurum, S.C., Israel, E., Montealegre, F., Wenzel, S.E., Peters, S.P., Meyers, D.A., and Bleecker, E.R. (2014) Effect of rare variants in ADRB2 on risk of severe exacerbations and symptom control during long-acting β agonist treatment in a multiethnic asthma population: a genetic study. *The Lancet Respiratory Medicine*, **2**, 204–213.

7 Roth, B.L. (2007) Drugs and valvular heart disease. *The New England Journal of Medicine*, **356**, 6–9.

8 Whitebread, S., Hamon, J., Bojanic, D. *et al.* (2005) *In vitro* safety pharmacology profiling: an essential tool for successful drug development. *Drug Discovery Today*, **10**, 1421–1433.

9 Hamon, J., Whitebread, S., Techer-Etienne, V., Le Coq, H., Azzaoui, K., and Urban, L. (2009) *In vitro* safety pharmacology profiling: what else beyond hERG? *Future Medicinal Chemistry*, **1**, 645–665.

10 Bowes, J., Brown, A.J., Hamon, J. *et al.* (2012) Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling. *Nature Reviews. Drug Discovery*, **11**, 909–922.

11 Azzaoui, K., Hamon, J., Faller, B., Whitebread, S., Jacoby, E., Bender, A., Jenkins, J.L., and Urban, L. (2007) Modeling promiscuity based on *in vitro* safety pharmacology profiling data. *ChemMedChem*, **2**, 874–880.

12 Nash, P.D. (2012) Why modules matter. *FEBS Letters*, **586**, 2572–2574.

13 Suh, D.C., Woodall, B.S., Shin, S.K., and Hermes-De Santis, E.R. (2000) Clinical and economic impact of adverse drug reactions in hospitalized patients. *Annals of Pharmacotherapy*, **34**, 1373–1379.

14 Sullivan, P.W., Valuck, R., Saseen, J., and MacFall, H.M. (2004) A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. *CNS Drugs*, **18**, 911–932.

15 Gautier, S., Bachelet, H., Bordet, R., and Caron, J. (2003) The cost of adverse drug reactions. *Expert Opinion on Pharmacotherapy*, **4**, 319–326.

16 US FDA (2014) Preventable Adverse Drug Reactions: A Focus on Drug Interactions. ADRs: Prevalence and Incidence. Available at http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm (accessed December 2, 2014).

17 US FDA (2014) FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files. Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm (accessed December 2, 2014).

18 Hocking, C.M., Townsend, A.R., and Price, T.J. (2013) Panitumumab in metastatic colorectal cancer. *Expert Review of Anticancer Therapy*, **13**, 781–793.

19 Urban, L., Whitebread, S., Hamon, J., Mikhailov, D., and Azzaoui, K. (2011) Screening for safety-relevant off-target activities, in *Polypharmacology* (ed. U.-J. Peters), John Wiley & Sons, Inc., Hoboken, NJ.

20 Muller, P.Y. and Milton, M.N. (2012) The determination and interpretation of the therapeutic index in drug development. *Nature Reviews. Drug Discovery*, **11**, 751–761.

21 Gu, Q., Dillon, C.F., and Burt, V.L. (2010) Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. *NCHS Data Briefs*, 42, 1–8.

22 De Hert, M., Detraux, J., van Winkel, R., Yu, W., and Correll, C.U. (2011) Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature Reviews Endocrinology*, **8**, 114–126.

23 Pepersack, T., Gilles, C., Petrovic, M., Spinnewine, A., Baeyens, H., Beyer, I., Boland, B., Dalleur, O., De Lepeleire, J., Even-Adin, D., Van Nes, M.C., Samalea-Suarez, A., and Somers, A. (Working Group Clinical Pharmacology,

Pharmacotherapy and Pharmaceutical Care; Belgian Society for Gerontology and Geriatrics) (2013) Prevalence of orthostatic hypotension and relationship with drug use amongst older patients. *Acta Clinica Belgica*, **68**, 107–112.

24 Woolcott, J.C., Richardson, K.J., Wiens, M.O., Patel, B., Marin, J., Khan, K.M., and Marra, C.A. (2009) Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Archives of Internal Medicine*, **169**, 1952–1960.

25 Hu, Y. and Bajorath, J. (2013) Compound promiscuity: what can we learn from current data? *Drug Discovery Today*, **18**, 644–650.

26 Ghoreschi, K., Laurence, A., and O'Shea, J.J. (2009) Selectivity and therapeutic inhibition of kinases: to be or not to be? *Nature Immunology*, **10**, 356–360.

27 Cox, K.J., Shomin, C.D., and Ghosh, I. (2011) tinkering outside the kinase ATP box: allosteric (type IV) and bivalent (type V) inhibitors of protein kinases. *Future Medicinal Chemistry*, **3**, 29–43.

28 Besnard, J., Ruda, G.F., Setola, V., Abecassis, K., Rodriguiz, R.M., Huang, X.P., Norval, S., Sassano, M.F., Shin, A.I., Webster, L.A., Simeons, F.R., Stojanovski, L., Prat, A., Seidah, N.G., Constam., D.B., Bickerton, G.R., Read, K.D., Wetsel, W.C., Gilbert, I.H., Roth, B.L., and Hopkins, A.L. (2012) Automated design of ligands to polypharmacological profiles. *Nature*, **492**, 215–220.

29 US FDA (2007) Antidepressant Use in Children, Adolescents, and Adults. Available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm (accessed December 2, 2014).

30 Center for Drug Evaluation and Research (CDER) (2012) Micardis (Telmisartan) Tablets. Detailed View: Safety Labeling Changes Approved by FDA. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm266672.htm (accessed December 2, 2014).

31 Mansfield, L.E. (2006) Once-daily immediate-release fexofenadine and sustained-release pseudoephedrine combination: a new treatment option for allergic rhinitis. *Expert Opinion on Pharmacotherapy*, **7**, 941–951.

32 US FDA (2014) How does FDA decide when a drug is not safe enough to stay on the market? Available at http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194984.htm (accessed December 2, 2014).

33 Roth, B.L. (2007) Drugs and valvular heart disease. *The New England Journal of Medicine*, **356**, 6–9.