Antitargets

Prediction and Prevention of Drug Side Effects

Edited by
Roy J. Vaz and Thomas Klabunde

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Series Editors

Prof. Dr. Raimund Mannhold
Molecular Drug Research Group
Heinrich-Heine-Universität
Universitätsstrasse 1
40225 Düsseldorf
Germany
mannhold@uni-duesseldorf.de

Prof. Dr. Hugo Kubinyi
Donnersbergerstrasse 9
67256 Weisenheim am Sand
Germany
kubinyi@t-online.de

Prof. Dr. Gerd Folkers
Collegium Helveticum
STW/ETH Zurich
8092 Zurich
Switzerland
folkers@collegium.ethz.ch

Volume Editors

Dr. Roy J. Vaz
Sanofi-Aventis
Route 202-206
Bridgewater, NJ 08807
USA
Roy.Vaz@sanofi-aventis.com

Dr. Thomas Klabunde
Sanofi-Aventis Deutschland
Industriepark Höchst G878
65926 Frankfurt
Germany
Thomas.Klabunde@sanofi-aventis.com

Cover Illustration
The cover shows a model of the hERG ion channel in the lower left (chapter 4), a CYP structure, lower right (chapter 10), a pharmacophore model for the alpha1a adrenergic receptor, upper right (chapter 6) and a schematic of the intestinal epithelium with some transporters, upper left (chapter 15).

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Contents

List of Contributors

Yasmin Aristei
University of Perugia
Chemistry Department
Laboratory for Chemometrics
and Cheminformatics
Via Elce di Sotto 10
06123 Perugia
Italy

Oren M. Becker
Epix Pharmaceuticals Ltd.
3 Hayetzira St.
Ramat Gan 52521
Israel

Current address:
Dynamix Pharmaceuticals
12 Motza Ha-Qetana
Mevasserei Zion 90805
Israel

Paolo Benedetti
Molecular Discovery Ltd
215 Marsh Road
Pinner, Middlesex
HA5 5NE London
United Kingdom

Emanuele Carosati
University of Perugia
Chemistry Department
Laboratory for Chemometrics
and Cheminformatics
Via Elce di Sotto 10
06123 Perugia
Italy

Andrea Cavalli
Department of Pharmaceutical Sciences
University of Bologna
Via Belmeloro 6
40126 Bologna
Italy

Sergio Clementi
University of Perugia
Chemistry Department
Laboratory for Chemometrics
and Cheminformatics
Via Elce di Sotto 10
06123 Perugia
Italy

Patrizia Crivori
Nerviano Medical Sciences
Accelera, Pharmacokinetic & Modeling/
Modeling
Viale Pasteur 10
20014 Nerviano
Italy

Gabriele Cruciani
University of Perugia
Chemistry Department
Laboratory for Chemometrics
and Cheminformatics
Via Elce di Sotto 10
06123 Perugia
Italy

Sarah Dalibalta
University of Leicester
Department of Cell Physiology and
Pharmacology
Medical Sciences Building
University Road
Leicester LE1 9HN
United Kingdom

Pier G. De Benedetti
University of Modena and Reggio Emilia
Department of Chemistry and
Advanced Scientific
Computing Laboratory
Via Campi 183
41100 Modena
Italy

Fabrizio De Ponti
University of Bologna
Department of Pharmacology
Via Irnerio 48
40126 Bologna BO
Italy

Philippe Dupuis
Cerep SA
Le bois l'Eveque
86600 Celle L'Evescault
France

Scott D. Edmondson
Merck Research Laboratories
Department of Medicinal Chemistry
P.O. Box 2000, RY123-234
Rahway, NJ 07065
USA

Andreas Evers
Sanofi-Aventis Deutschland GmbH
Chemical Analytical Sciences
Drug Design
Building G838
65926 Frankfurt am Main
Germany

Francesca Fanelli
University of Modena and Reggio Emilia
Dulbecco Telethon Institute and
Department of Chemistry
Via Campi 183
41100 Modena
Italy

Martin F. Fromm
University of Erlangen-Nuremberg
Institute of Experimental and Clinical
Pharmacology and Toxicology
Fahrstr. 17
91054 Erlangen
Germany

Hartmut Glaeser
University of Erlangen-Nuremberg
Institute of Experimental and Clinical
Pharmacology and Toxicology
Fahrstr. 17
91054 Erlangen
Germany

Craig Jamieson
Organon Laboratories Ltd
Medicinal Chemistry
Newhouse
Lanarkshire
ML1 5SH
United Kingdom

Dooseop Kim
Merck Research Laboratories
Department of Medicinal Chemistry
P.O. Box 2000, RY800-C206
Rahway, NJ 07065
USA

Thomas Klabunde
Sanofi-Aventis Deutschland GmbH
Science & Medical Affairs
Drug Design
Building G878
65926 Frankfurt am Main
Germany

Jörg König
University of Erlangen-Nuremberg
Institute of Experimental and Clinical
Pharmacology and Toxicology
Fahrstr. 17
91054 Erlangen
Germany

Christian Laggner
University of Innsbruck
Department of Pharmaceutical
Chemistry
CAMD Group
Innrain 52c
6020 Innsbruck
Austria

Thierry Langer
University of Innsbruck
Department of Pharmaceutical
Chemistry
CAMD Group
Innrain 52c
6020 Innsbruck
Austria

Jonathan S. Mason
Lundbeck Research
Ottiliavej 9
2500 Valby
Denmark

Jacques Migeon
Cerep SA
Le bois l'Eveque
86600 Celle L'Evescault
France

John S. Mitcheson
University of Leicester
Department of Cell Physiology and
Pharmacology
Medical Sciences Building
University Road
Leicester LE1 9HN
United Kingdom

Elizabeth M. Moir
Organon Laboratories Ltd
Medicinal Chemistry
Newhouse
Lanarkshire
ML1 5SH
United Kingdom

Annie Otto-Bruc
Cerep SA
Le bois l'Eveque
86600 Celle L'Evescault
France

Sonia Maria Poli
Addex Pharma
Non-Clinical Development
12, Chemin des Aulx
1228 Plan-Les-Ouates – GE
Switzerland

Zoran Rankovic
Organon Laboratories Ltd
Medicinal Chemistry
Newhouse
Lanarkshire
ML1 5SH
United Kingdom

Maurizio Recanatini
University of Bologna
Department of Pharmaceutical Sciences
Via Belmeloro 6
40126 Bologna
Italy

Dan Rock
Amgen Inc.
1201 Amgen Court West
Seattle, WA 98119
USA

Bryan L. Roth
UNC Chapel Hill School of Medicine
Medicinal Chemistry
Burnett Womack Building; Room 8032
UNC Chapel Hill
Chapel Hill, NC
USA

Daniela Schuster
University of Innsbruck
Department of Pharmaceutical Chemistry
CAMD Group
Innrain 52c
6020 Innsbruck
Austria

Vincent Setola
INSERM
U616 Hôpital Pitié-Salpêtrière
Paris
France

Theodora M. Steindl
Inte:Ligand Softwareentwicklungs- und Consulting GmbH
Clemens-Maria-Hofbauer-G. 6
2344 Maria Enzersdorf
Austria

Riccardo Vianello
Molecular Discovery Ltd
215 Marsh Road, Pinner
Middlesex
HA5 5NE London
United Kingdom

Jan Wahlstrom
Amgen Inc.
1201 Amgen Court West
Seattle, WA 98119
USA

Larry Wienkers
Amgen Inc.
1201 Amgen Court West
Seattle, WA 98119
USA

Grant Wishart
Organon Laboratories Ltd
Medicinal Chemistry
Newhouse
Lanarkshire
ML1 5SH
United Kingdom

Wen Xie
University of Pittsburgh
Center for Pharmacogenetics
633 Salk Hall
Pittsburgh, PA 15216
USA

Ismael Zamora
Pompeu Fabra University
GRIB-IMIM
Dr Aiguader 80
E080003 Barcelona
Spain

Yonggong Zhai
Beijing Normal University
Biomedicine Research Institute and College of Life Science
Beijing 100875
China

Jie Zhou
University of Pittsburgh
Center for Pharmacogenetics
633 Salk Hall
Pittsburgh, PA 15216
USA

Preface

When the hammer hits your thumb in addition to, or instead of the nail - this clearly is an antitarget problem. In drug action and especially in drug-drug interactions, the situation is much more serious. There are numerous targets which should not be activated, induced, or inhibited by a drug. Adverse drug reactions (ADRs) are estimated to be one of the leading causes of morbidity and mortality in healthcare. Especially older patients receive up to 15 different medications, and even more, at the same time – no wonder that unfavorable drug-drug interactions happen, considering also the poor physical condition of such patients. In January 2000, the Institute of Medicine reported that in the US about 7000 deaths per year occur due to ADRs; the number may be even much larger, not to count the manyfold non-fatal side effects.

In defining the term "antitarget" one runs into some problems. Let us start with terfenadine, a non-sedating H1-antihistaminic. In its clinical studies it was obviously safe, with only minor side effects. However, after its broad therapeutic use it turned out to produce fatal arrhythmias. In addition to being an H1 antagonist, terfenadine is a potent hERG channel inhibitor. Under normal conditions, terfenadine is already metabolized in the intestinal wall; no measurable plasma levels and no cardiac side effects are observed. If CYP inhibitors prevent terfenadine metabolism, cardiac toxicity results. Thus, in addition to its H1 receptor antagonism, the compound inhibits the hERG channel, a most prominent antitarget. The terfenadine problem could be circumvented by replacing the compound by its active metabolite fexofenadine, which is not any longer a hERG channel inhibitor.

Already around 1990, David Bailey discovered that grapefruit (but not orange) juice significantly increases the bioavailability of some drugs, for example the calcium channel blockers felodipine and nifedipine. After some problems to publish this highly surprising observation, his manuscript was accepted by Lancet and many reports followed for other drugs. The whole story shall not be elaborated here in detail but it remains the question: is CYP3A4, which is inhibited by some flavonoid and furocoumarin constituents of grapefruit juice, an antitarget? It is: despite the fact that increase in bioavailability is a desirable effect, individual variation is too large to be of therapeutic value. Only in the case of clinically monitored drugs, for example cyclosporin, the co-medication of a CYP3A4 inhibitor, for example ketoconazole, is used to reduce the dose of this expensive drug.

Recently it was discovered that grapefruit juice also induces the expression of intestinal drug transporters. With fexofenadine, the safe replacement of terfenadine, the paradox situation results that bioavailability of this drug decreases (!) after intake of grapefruit juice, due to induction of an efflux pump, the organic anion-transporting polypeptide 1A2 (OATP1A2). Kirby and Unadkat commented this paradox by asking the question "Grapefruit juice, a glass full of drug interactions?"

Not only food constituents but also OTC drugs may cause significant drug-drug interactions. One of the well-known examples is St. John's Wort (*Hypericum perforatum* L.) extract, supposed to be beneficial against mild depression. However, in addition to the phototoxic agent hypericin, the plant contains hyperforin, the strongest inducer of CYPs (especially CYP3A4) and drug transporters. In this manner, self-medication with St. John's Wort reduces the bioavailability and thus the activity of several drugs, whereas doses of some drugs have to be reduced after discontinuation of this extract because CYP and transporter levels return to normal.

There are many more antitargets, prominent ones being several G protein-coupled receptors. Thus, it is high time that a book on antitargets becomes available and we, as Editors of the series Methods and Principles in Medicinal Chemistry, are very much indebted to Roy Vaz and Thomas Klabunde, leading scientists in antitarget research, for editing such a monograph. The book starts with an introduction on the reasons why drugs fail in the clinics or after market introduction and a chapter on ADME and side effects prediction. The main two sections contain several chapters on antitargets and side effects (hERG channel and GPCR antitargets) and on antitargets in ADME (CYPs and drug transporters). The book concludes with some case studies of drug optimization against antitargets.

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Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zürich

A Personal Foreword

A single report of a drug reaction in a 39-year-old woman ultimately contributed to the removal of the allergy drug Seldane (terfenadine) from the market in 1998 [1]. Doctors at the National Naval Medical Center in Bethesda, Md., admitted the woman to the hospital because of fainting episodes. She had been prescribed Seldane (terfenadine) 10 days before. She also started using the prescription drug Nizoral (ketoconazole) for a vaginal yeast infection. That combination caused potentially fatal changes in her heart rhythm. The Food and Drug Administration (FDA) issued warnings indicating that ketoconazole interfered with terfenadine's metabolism, which resulted in increased levels of terfenadine in the blood and slowed its elimination from the body. The FDA also warned that a similar effect could occur if Seldane was taken with the antibiotic erythromycin.

Thus the first awareness of antitargets was brought to the forefront with the withdrawal of terfenadine. Ketoconazole is a strong inhibitor of CYP3A4, which is also the primary enzyme responsible for the clearance of terfenadine. The inhibition of CYP3A4 leads to the increase in concentration of terfenadine in the blood. Terfenadine itself is a blocker of the ion channel hERG (human ether-a-go-go related gene) and caused a prolonged QT, leading to Torsades de Pointes and possibly death. Also ketoconazole inhibits the efflux transporter P-glycoprotein (P-gp) or MDR1 (multidrug resistance protein), for which terfenadine is a substrate. Hence when co-administered with ketoconazole, the concentration of terfenadine in blood would be much higher than if taken without other drugs such as ketoconazole. Therefore inhibition of both P-gp and CYP3A4 could lead to drug-drug interactions and inhibition of hERG either by the compound itself or its metabolite.

The example of terfenadine shows that toxic effects can be either induced directly by the action of a drug or a drug metabolite on an antitarget like the hERG channel. In addition, certain transporters and metabolizing enzymes, like P-gp and CYP3A4, need also be considered as antitargets as blocking their activity can change the concentration of a co-administered drug or its metabolite in blood, thus causing drug-drug interactions and potential toxicity.

Adverse drug reactions (ADRs) cost approximately one hundred and thirty nine billion dollars annually [2–4] in the United States. This number is larger than the

cost of cardiovascular or diabetic care. ADRs cause 1 out of 5 injuries or deaths per year to hospitalized patients and the mean length of stay, the cost and the mortality for patients admitted due to an ADR are double that for control patients. Many ADRs are due to off-target and antitarget interactions. Some of these have lead to withdrawal of the drug(s) from the marketplace.

Since terfenadine, there have been other market withdrawals of drugs. As shown in the first chapter of the book the main cause for the 16 drug withdrawals from 1992 to 2002 was toxicity, mainly cardiovascular toxicity or hepatotoxicity. Only recently Vioxx (rofecoxib) had to be withdrawn from the market. In contrast to terfenadine, where the molecular mechanism of its side effects has been fully understood, the underlying mechanism by which rofecoxib, a selective cyclooxygenase 2 inhibitor that exhibits cardiovascular effects is still unclear [5]. Pondimin (fenfluramine), a serotonergic anorectic, was withdrawn in 1997 due to the risk of development of primary pulmonary hypertension or valvular heart disease. The first case of fenfluramine associated valvular heart disease discovered 7 years after discontinuation of treatment and requiring double valve replacement 2 years later has just been reported [6]. For fenfluramine the mechanism by which it causes valvular heart disease has recently been uncovered showing a causal association between agonism on the G-protein coupled receptor (GPCR) 5-HT_{2B} and valvular heart disease (Chapter 7 in the book).

According to FDA experts, discovering terfenadine's interactions with other drugs marked a significant advance. These and other discoveries improved the ability of the FDA and drug manufacturers to test for drug interactions and to investigate risks of heart rhythm abnormalities and other toxicities before drugs could be marketed. In addition, unraveling the mechanism of drug toxicities and identifying specific channels, receptors including nuclear receptors, transporters or enzymes as antitargets enabled establishment of *in vitro* test systems to monitor potential antitarget mediated side effects and toxicity in the drug discovery phase. The list of antitargets is still being compiled but the events that have lead to the discovery of the known antitargets has impacted the way research is conducted during drug discovery today.

In every family of biological targets there are antitargets. In this book, we have avoided discussion of kinases, which are still controversial as non-oncology targets and could probably command several chapters or volumes. Transporters and metabolizing enzymes like CYP450s that can mediate undesired drug-drug interactions have been mentioned before. In the area of potassium voltage-gated ion channels, there are therapeutic targets such as Kv1.3 and Kv1.5 but at the same time there are antitargets such as hERG. GPCRs form a large protein family that plays an important role in many physiological and patho-physiological processes. Especially the subfamily of biogenic amine binding GPCRs has provided excellent drug targets for the treatment of numerous diseases [7]. Although representing excellent therapeutic targets, the central role that many of the biogenic amine binding GPCRs play in cell signaling also poses a risk on new drug candidates which reveal side-affinities towards these receptor sites: These candidates bear the risk to interfere with the physiological signaling process and to cause undesired effects in preclinical or

clinical studies. Besides the 5-HT_{2B} receptor mentioned before, the α_{1A} adrenergic receptor, being a drug target for the treatment of benign prostatic hypertrophy (BPH), has been suggested as an antitarget at the same time that mediates cardiovascular side-effects of many drug candidates causing orthostatic hypotension, dizziness and fainting spells [8]. Other examples of GPCR antitargets are the muscarinic M1 receptor correlated with attention and memory deficits or the serotonin 5-HT_{2C} receptor associated with weight gain. As shown in one of the introductory chapters of this book, correlation between *in vitro* affinity and *in vivo* adverse effects can currently be recognized by profiling, hundreds of drugs with known ADRs using large panels of pharmacological *in vitro* assays.

There are several references made to both off-targets as well as antitargets in the literature. In this book we will primarily be attempting to cover the topic of antitargets. Off-target activity the way we interpret it, is activity for a particular compound towards a target that was not anticipated, when it was synthesized or isolated. For example, compounds that are designed or synthesized for activity towards serine proteases (not for thrombosis) are not expected to have any activity towards serine protease targets such as thrombin or others in the coagulation pathway, which could be anti-thrombotic targets themselves. The term off-targets includes antitargets and the off-target activities could be beneficial or detrimental. Antitargets on the other hand are targets that are detrimental towards progression of the compound towards becoming a drug.

Within recent years the understanding of the molecular interactions between antitargets and drugs or drug candidates has tremendously increased allowing *in silico* antitarget models to be established. 3-dimensional structures of several antitargets (often in complex with inhibitors) are now available either derived by homology modeling (e.g. the hERG channel or GPCRs) or by protein crystallography (e.g. cytochrome P450s). Structural chemical motifs often associated with antitarget interactions (e.g. for cytochrome P450 binding or inhibition) have been captured in knowledge databases. Computational models like 3D-pharmacophore or 3D-QSAR models (e.g. for GPCRs, hERG, CYPs, P-gp) have been established to not only recognize antitarget affinities in chemical lead series but also to guide the chemical optimization of these leads towards development candidates lacking undesired antitarget side affinities and thus potential side effects or toxicities. These models are captured – together with introductory chapters on the biological aspects – in the second (focusing on ion channels and GPCRs) and the third section of this book (describing antitargets mediating drug-drug interactions).

Examples of optimization of selectivity towards the antitargets have been well described in the recent literature such as illustrated in Gao et al. [9] and Kuduk *et al.* [10]. In the last section we have tried to include very specific case studies of successful drugs for which optimization of selectivity towards specific or general antitargets were successfully negotiated, e.g. for Januvia (chapter 17), a recently released DPP4 inhibitor or for PRX-00023, a selective 5-HT_{1A} agonist currently in phase IIb clinical trials (chapter 19).

We would first thank the editors of the series for enabling this volume in the Methods and Principles in Medicinal Chemistry series. We would like to sincerely

thank all chapter authors for making this book a reality. We would like to acknowledge their great enthusiasm in preparing their manuscripts and the high quality of their contributions. It has been a pleasure working with each and every one of them. The editors are also grateful to Frank Weinreich, Nicola Oberbeckmann-Winter and the staff of Wiley-VCH for their excellent support in the production of this book. We also thank the Sanofi-Aventis Discovery Management for enabling this book. We thank our families for putting up with us during the last few months.

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Roy Vaz, Bridgewater
Thomas Klabundl, Frankfurt

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I
General Aspects

1
Why Drugs Fail – A Study on Side Effects in New Chemical Entities

Daniela Schuster, Christian Laggner, Thierry Langer

1.1
Introduction

Drug development is a long and cost-intensive business. Only after years of lead identification, chemical optimization, *in vitro* and animal testing can the first clinical trials be conducted. Unfortunately, many projects still fail in this late stage of development after a considerable amount of money has been spent. According to estimates, preapproval costs for a new drug exceed US$ 800 million [1].

Approximately 10% of new chemical entities (NCEs) show serious adverse drug reactions (ADRs) after market launch. Such events usually result in 'new black box warnings' by the US Food and Drug Administration (FDA), label change or market withdrawal. The most common causes for these actions are hepatic toxicity, hematologic toxicity and cardiovascular toxicity [2]. Reasons for such ADRs, which are identified only after NCEs are launched on the market, include the narrow spectrum of clinical disorders and participating patient profiles in clinical studies as well as the fact that serious ADRs are often rare and that the number of patient exposures required to identify such occurrences sometimes may range over a few millions [3].

To avoid the occurrence of ADRs in the future, specific trials to detect them should therefore be conducted before an NCE is launched on the market. Before this can be done, however, the major reasons leading to the withdrawal of drugs and termination of NCE-to-drug development should be identified and analyzed.

In this chapter, reasons why 17 drugs were withdrawn from the Western market between 1992 and 2006 are discussed and facts on 63 terminated clinical development projects presented, so as to identify the most common reasons for the failure of drugs in this late stage of drug development. This analysis is then compared with two previous related studies published more than 18 years ago by Prentis *et al.* [4] and Kennedy [5].

The study by Prentis *et al.* [4] included an analysis of 198 NCEs, developed between 1964 and 1985 by British pharmaceutical companies but had not been marketed for reasons presented in Figure 1.1. Kennedy [5] further analyzed these data and noticed that a high number of anti-infective drug development projects were all terminated

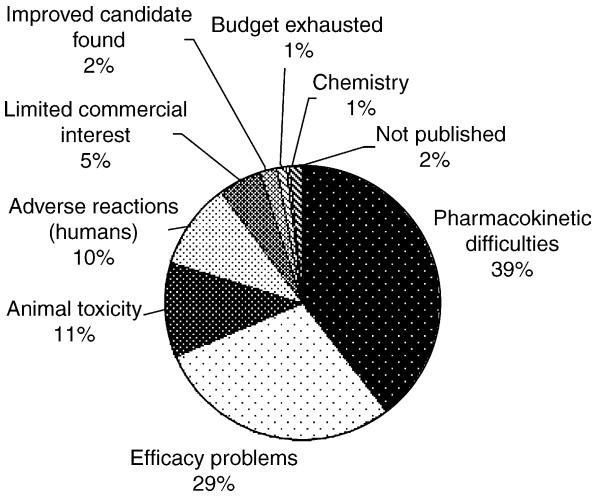

Figure 1.1 Reasons for drug development termination from 1964 to 1985 ($n = 198$).

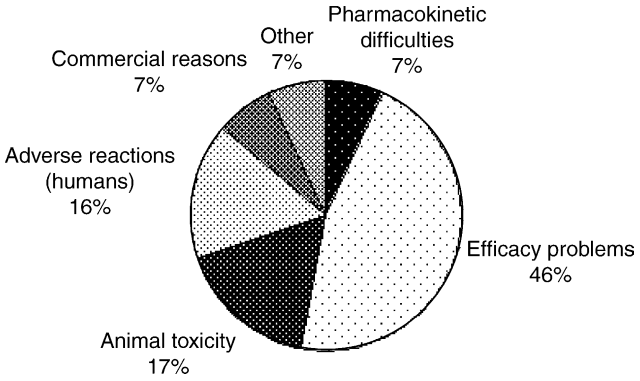

Figure 1.2 Reasons for drug development termination, excluding anti-infectives ($n = 121$).

because of pharmacokinetic difficulties. He therefore excluded the anti-infective NCEs from the statistics and presented the facts as illustrated in Figure 1.2.

1.2
Drugs Withdrawn from the Market between 1992 and 2006 Listed Alphabetically

1.2.1
Amineptine

The atypical tricyclic antidepressant amineptine (Survector) is an indirect dopamine agonist, which selectively inhibits dopamine uptake and induces its release, with additional stimulation of the adrenergic system. Its antidepressant effects are similar to those of other tricyclic antidepressant drugs. However, it acts more rapidly, is better