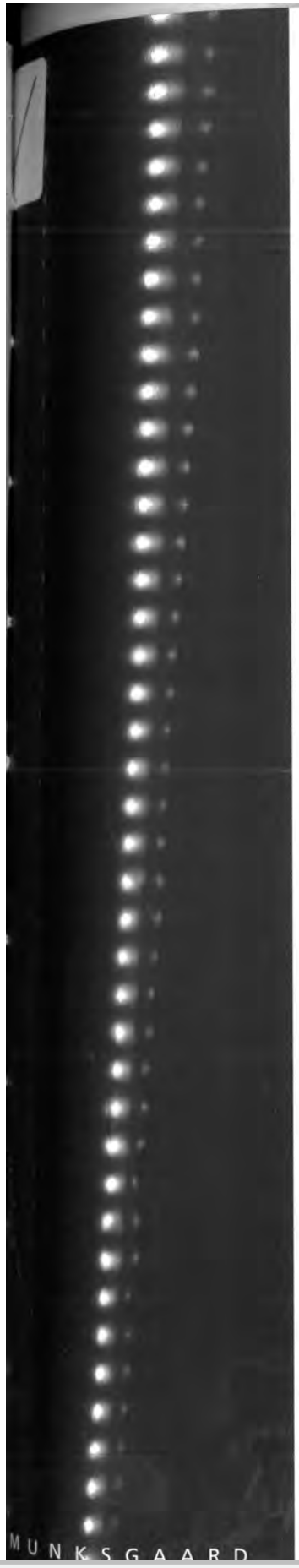

Acta Psychiatrica Scandinavica

MUNKSGAARD

VOLUME 104 NO 3 SEPTEMBER 2001

Acta Psychiatrica Scandinavica

EDITOR'S ADDRESS:
Department of Psychiatric Demography
Institute for Basic Psychiatric Research
Psychiatric Hospital in Aarhus
Aarhus University Hospital
DK-8240 Risskov, Denmark
Fax: +45 77 89 28 99
E-mail: bct@psykiatri.aaa.dk

ASSISTANT TO THE EDITOR:
Rasmus W. Licht,
Risskov, Denmark

EDITORIAL SECRETARY:
Birgitte Christiansen
Risskov, Denmark

EDITOR:
Povl Munk-Jørgensen,
Risskov, Denmark

AIM AND SCOPE

The aim of Acta Psychiatrica Scandinavica is to publish articles in English of high scientific quality representing clinical and experimental work in psychiatry. The scope is to act as an international forum for the dissemination of information advancing the science and practice of psychiatry. Original articles are welcomed, especially those that bring new knowledge or extend the present understanding of mental disorders. Parallel to original articles priority is given to review articles.

Articles requiring rapid publication because of their significance and timeliness may be included as Short communications not exceeding two printed pages. Debate within psychiatry is encouraged in the form of Letters to the editor. All manuscripts published have been assessed by two experienced referees.

SUBSCRIPTION

Two volumes of six issues are published each year. Subscription price 2001 including postage: Paper only: DKK 3900 (USD 520). Online only: DKK 3510 (USD 468). Combined paper and online: DKK 4290 (USD 572). All prices are payable in advance and subject to exchange rate fluctuations. Supplements to current volumes will be supplied to the subscribers at no extra charge.

Subscription orders may be placed with:

Head office
MUNKSGAARD
International Publishers Ltd.
35 Nørre Søgade
P.O. Box 2148
DK-1016 Copenhagen K
Denmark
Tel: +45 77 33 33 33
Fax: +45 77 33 33 77
E-mail: customerservice@munksgaard.dk
http://journals.munksgaard.dk/actapsych

OR

Regional office in USA
MUNKSGAARD
International Publishers Ltd.
Commerce Place
350 Main Street
Malden, MA 02148-5018
USA
Tel: (781) 388-8273
Fax: (781) 388-8274

or with any subscription agent. Advertising orders should be sent to the publisher (head office).

Important - for subscriptions delivered to addresses within the European Union. If you have a VAT registration number, you must provide this. Otherwise, please add your local VAT on journals to the above price in DKK: Austria 10%, Belgium 6%, Denmark 25%, Finland 0%, France 2.1%, Germany 7%, Greece 4%, Ireland 12.5%, Italy 4%, Luxembourg 3%, the Netherlands 6%, Portugal 5%, Spain 4%, Sweden 25%, UK 0%. Canada: Please add 7% GST.

Acta Psychiatrica Scandinavica (ISSN 0001-690X) is published monthly by Munksgaard International Publishers Ltd, 35 Nørre Søgade, P.O. Box 2148, DK-1016 Copenhagen K, Denmark. Periodicals postage paid at Champlain NY and additional mailing offices. USA Postmaster for North American subscribers: Send address changes to IMS of NY, P.O. Box 1518, Champlain NY-12919. (USPS#014-330) Airspeed and mailing in the USA by INSA. Printed in England by The Charlesworth Group, Huddersfield.

Acta Psychiatrica Scandinavica

VOLUME 104
NUMBER 3
SEPTEMBER 2001

Abstracted or indexed in: Biological Abstracts/BIOSIS, ADONIS, Chemical Abstracts, Science Citation Index, Social Sciences Citation Index, SCISEARCH, Research Alert, Medical Documentation Service, Current Contents: Life Sciences; Clinical Medicine, Social & Behavioral Sciences, EMBASE/Excerpta Medica, Elsevier BTOBASE/Current Awareness in Biological Sciences, Criminology, Penology & Police Science Abstracts. Index Medicus/MEDLINE.

MUNKSGAARD . COPENHAGEN

Acta Psychiatr Scand 2001: 104: 173–192
Printed in UK. All rights reserved

ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

Review article

CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages

Kirchheiner J, Brøsen K, Dahl ML, Gram LF, Kasper S, Roots I, Sjöqvist F, Spina E, Brockmöller J. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages.
Acta Psychiatr Scand 2001: 104: 173–192. © Munksgaard 2001.

Objective: This review aimed to provide distinct dose recommendations for antidepressants based on the genotypes of cytochrome P450 enzymes CYP2D6 and CYP2C19. This approach may be a useful complementation to clinical monitoring and therapeutic drug monitoring.
Method: Our literature search covered 32 antidepressants marketed in Europe, Canada, and the United States. We evaluated studies which had compared pharmacokinetic parameters of antidepressants among poor, intermediate, extensive and ultrarapid metabolizers.
Results: For 14 antidepressants, distinct dose recommendations for extensive, intermediate and poor metabolizers of either CYP2D6 or CYP2C19 were given. For the tricyclic antidepressants, dose reductions around 50% were generally recommended for poor metabolizers of substrates of CYP2D6 or CYP2C19, whereas differences were smaller for the selective serotonin reuptake inhibitors.
Conclusion: We have provided preliminary average dose suggestions based on the phenotype or genotype. This is a first attempt to apply the new pharmacogenetics to suggest dose-regimens that take the differences in drug metabolic capacity into account.

J. Kirchheiner[1], K. Brøsen[2], M. L. Dahl[3], L. F. Gram[2], S. Kasper[4], I. Roots[1], F. Sjöqvist[3], E. Spina[5], J. Brockmöller[6]

[1]Institute of Clinical Pharmacology, Charité, Humboldt University of Berlin, Berlin, Germany, [2]Institute of Public Health, Clinical Pharmacology, Odense, Denmark, [3]Department of Clinical Pharmacology, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden, [4]Department of General Psychiatry, University of Vienna, Vienna, Austria, [5]Institute of Clinical Pharmacology, University of Messina, Messina, Italy and [6]Department of Clinical Pharmacology, Georg-August-University, Göttingen, Germany

Key words: polymorphism; antidepressant therapy; pharmacogenetics; cytochrome P-450; CYP2D6; CYP2C19

Prof. Dr Jürgen Brockmöller, Universitätsklinikum, Abteilung Klinische Pharmakologie, Robert-Koch-Str. 40, 37075 Göttingen, Germany
E-mail: jbrockm@gwdg.de

Accepted for publication 13 March, 2001

Introduction

Genetic factors have long been known to cause interindividual differences in pharmacokinetics, efficacy and adverse effects of antidepressant drugs (ADs) (1, 2). Numerous studies have now been performed on the impact of genetic polymorphisms in cytochrome P450 enzymes (CYP) on the disposition of antidepressant drugs. Particularly well characterized is the significant effect of the CYP2D6 and CYP2C19 polymorphisms on the pharmacokinetics of almost all tricyclic and many other antidepressants. The activities of these two enzymes are both bimodally distributed in the Caucasian population, allowing classification of individuals into extensive (EM) and poor (PM) metabolizers. The CYP2D6 polymorphism was discovered in the 1970s as sparteine and debrisoquine oxidation polymorphisms (3, 4). The CYP2C19 polymorphism was initially identified as S-mephenytoin hydroxylation polymorphism (5). The frequency of CYP polymorphisms has now been investigated in different populations and the allele frequencies have been found to differ substantially. Consideration of interethnic differences is therefore necessary (6, 7).

The effects of these polymorphisms on the clinical pharmacology of antidepressants have been reviewed previously (8–12). Poor metabolizers of CYP2D6 or CYP2C19 substrates may be more likely to suffer from adverse drug effects than extensive metabolizers when taking normal

doses of drugs that are active *per se* and are metabolized mainly via these pathways. The extent of these potential problems largely depends on the relative contribution of the respective CYP enzyme to the total elimination of the drug and the therapeutic index of the drug (12). The molecular genetic basis of CYP polymorphisms has been elucidated to an extent which allows a clinically useful prediction of a patient's drug metabolic phenotype (13–15). Such a genotyping before treatment has already earlier been postulated as a useful tool to prevent adverse effects, especially for drugs with a relatively narrow therapeutic range (16, 17). This information might be used in provision of average dose recommendations for different genetic subpopulations of patients. This may in turn provide therapeutic and pharmacoeconomic benefits (18, 19). Genetic analyses of the metabolizer status will become more common for clinicians in the future. Genotyping has the advantage that it needs to be performed only once in life for each patient and the costs of this analysis are lower than 1 day of stay in hospital. With current technology, such genotype analyses may be performed within a few hours. Analogous to the routinely used dose adjustment tables for the dosage of digoxin or aminoglycosides in patients with kidney disease, or analogous to dose adjustment tables used for the specific age groups in paediatrics, specific recommendations will be required about how to adjust the drug dosages to an individual's specific drug metabolic phenotype. For CYP2D6, the overall sensitivity of genotyping tests to predict the phenotypical poor metabolizer is more than 99% when testing for the common inactive alleles (*3, *4, *5, *6, *7, *8, *16) in the Caucasian population (15, 18, 20). Molecular genetic prediction of intermediate metabolizers (IM) was less accurate considering the allele variants given above, but precision of the identification of intermediate metabolizers may be improved considering CYP2D6 allele *2 variants (21). For CYP2C19, genotyping is able to identify between 93 and 100% of the phenotypic poor metabolizers (13, 22–26).

The goal of this review was to derive antidepressant dose recommendations based on drug metabolic pheno- or genotype and, if such data were not available, to identify priorities for further clinical studies. Since efficacy studies have not been performed for each genotype, we have assumed that equal plasma concentrations imply equal drug effects.

Dose adjustments based on the genotype of the polymorphic drug metabolizing enzymes are complicated by the existence of active metabolites that in turn are metabolized. We therefore provide references to several reviewers who have studied the role of active metabolites for the overall antidepressant effects (27–29). The elimination of antidepressants may be profoundly influenced by metabolic drug interactions. Several reviews focus on the inhibitory properties on drug metabolism of antidepressants, and especially elaborate on the prediction of metabolic drug interactions and the possibilities to avoid them (28, 27–38).

To adjust optimally for drug interactions and other factors such as compliance, age or liver function impairment, close clinical monitoring of the patients and therapeutic drug monitoring are the essential tools in dose optimization (39, 40). General problems in dose finding for antidepressant drugs have been discussed previously (41). There is little convincing evidence that different types of depression require different doses but in other conditions, such as pain, enuresis, anxiety, etc. the dose requirements may be different compared to depression (42). For the tricyclic antidepressants, early experiences with severe tolerability problems appear to have determined the rather cautious dosing policy often employed. Concentration effect studies revealed clear-cut relationships for some tricyclic antidepressants (imipramine, nortriptyline) which became the basis for recommended therapeutic drug monitoring procedures (43, 44). However, in general there appears to be no simple relationship between dosage, plasma concentration and clinical outcome of antidepressants as a whole. The newer antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine revealed flat and overlapping dose–effect curves for the antidepressant and adverse effects (45). Unfortunately, these dose–effect studies contain little information on the underlying pharmacokinetic and pharmacogenetic variability which may explain interpatient response variability on a given dose. Assessment of the genetically determined variability in drug concentration may indeed contribute to improve the therapeutic effect and reduce the risk of dropouts due to tolerability problems.

Methods of data analysis

Definitions and study inclusion criteria

We considered all studies on antidepressants except those on lithium, antipsychotics used in depression and on herbal drugs. We reviewed only studies conducted in humans, either healthy volunteers or patients, in which the pharmacokinetic and/or pharmacodynamic parameters of

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.