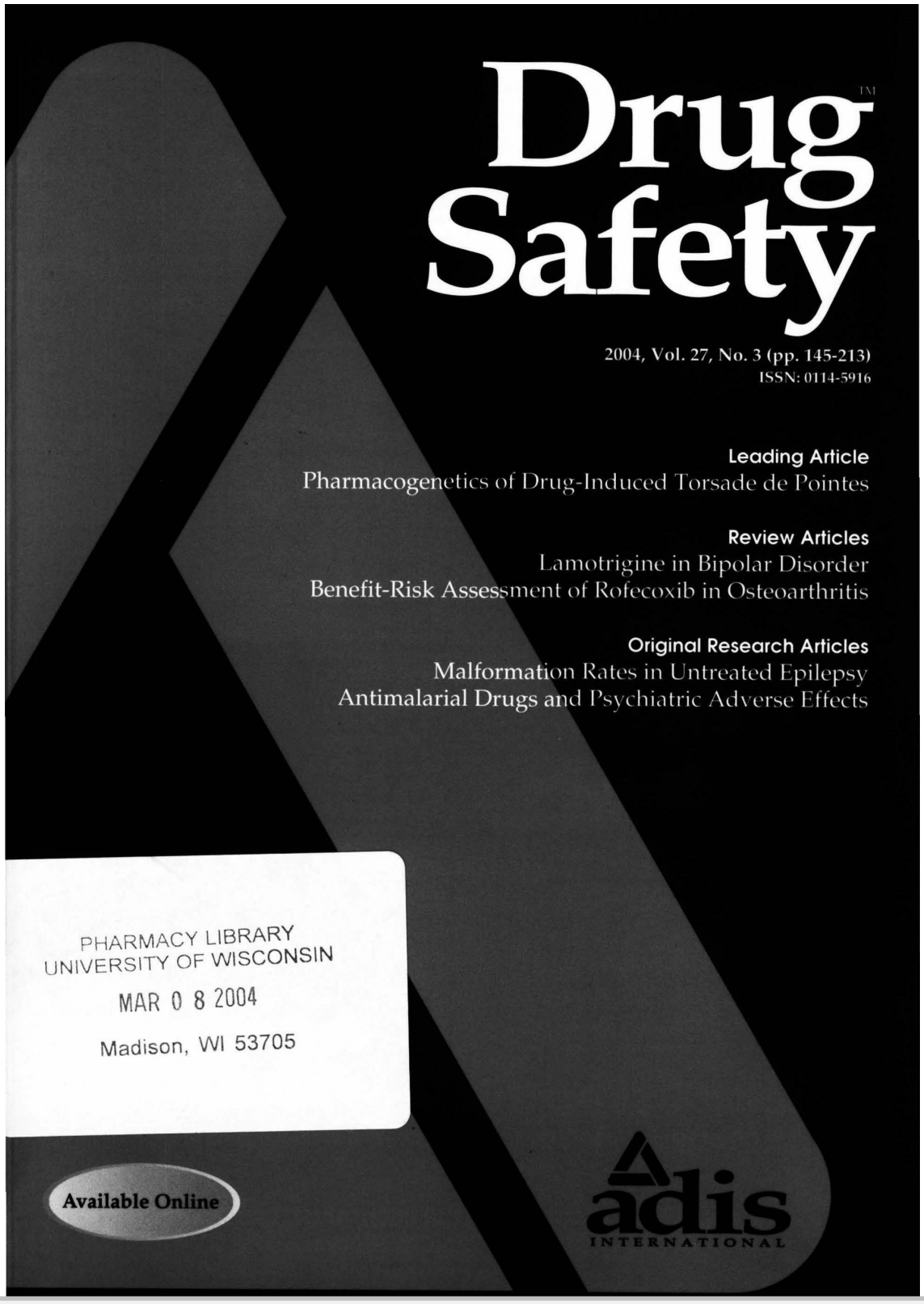

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Drug™ Safety

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Aim and Scope: *Drug Safety* advances the rational use of pharmacotherapy by providing a programme of review articles offering guidance for safe and effective drug utilisation and prescribing.
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Pharmacogenetic Aspects of Drug-Induced Torsade de Pointes

Potential Tool for Improving Clinical Drug Development and Prescribing

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Abstract

Drug-induced torsade de pointes (TdP) has proved to be a significant iatrogenic cause of morbidity and mortality and a major reason for the withdrawal of a number of drugs from the market in recent times. Enzymes that metabolise many of these drugs and the potassium channels that are responsible for cardiac repolarisation display genetic polymorphisms. Anecdotal reports have suggested that in many cases of drug-induced TdP, there may be a concealed genetic defect of either these enzymes or the potassium channels, giving rise to either high plasma drug concentrations or diminished cardiac repolarisation reserve, respectively. The presence of either of these genetic defects may predispose a patient to TdP, a potentially fatal adverse reaction, even at therapeutic dosages of QT-prolonging drugs and in the absence of other risk factors. Advances in pharmacogenetics of drug metabolising enzymes and pharmacological targets, together with the prospects of rapid and inexpensive genotyping procedures, promise to individualise and improve the benefit/risk ratio of therapy with drugs that have the potential to cause TdP. The qualitative and the quantitative contributions of these genetic defects in clinical cases of TdP are unclear because not all of the patients with TdP are routinely genotyped and some relevant genetic mutations still remain to be discovered.

There are regulatory guidelines that recommend strategies aimed at uncovering the risk of TdP associated with new chemical entities during their development. There are also a number of guidelines that recommend integrating pharmacogenetics in this process. This paper proposes a strategy for integrating pharmacogenetics into drug development programmes to optimise association studies correlating genetic traits and endpoints of clinical interest, namely failure of efficacy or development of repolarisation abnormalities. Until pharmacogenetics is carefully integrated into all phases of development of QT-prolonging drugs and large-scale studies are undertaken during their post-marketing use to determine the genetic components involved in induction of TdP, routine genotyping of patients remains unrealistic.

Even without this pharmacogenetic data, the clinical risk of TdP can already be greatly minimised. Clinically, a substantial proportion of cases of TdP are due to the use of either high or usual dosages of drugs with potential to cause TdP in the presence of factors that inhibit drug metabolism. Therefore, choosing the lowest effective dose and identifying patients with these non-genetic risk factors are important means of minimising the risk of TdP. In view of the common secondary pharmacology shared by these drugs, a standard set of contraindications and

warnings have evolved over the last decade. These include factors responsible for pharmacokinetic or pharmacodynamic drug interactions. Among the latter, the more important ones are bradycardia, electrolyte imbalance, cardiac disease and co-administration of two or more QT-prolonging drugs.

In principle, if large scale prospective studies can demonstrate a substantial genetic component, pharmacogenetically driven prescribing ought to reduce the risk further. However, any potential benefits of pharmacogenetics will be squandered without any reduction in the clinical risk of TdP if physicians do not follow prescribing and monitoring recommendations.

Prescribing drugs during routine clinical practice is a relatively empirical trial and error process consisting of selecting a drug and recommending a relatively rigid 'standard' dose schedule for every patient. These dose schedules, investigated during drug development, are based on population mean data and usually ignore the large interindividual variability that is present within a population.

The International Conference on Harmonisation (ICH) guideline[1] on 'Dose-Response Information to Support Drug Registration' recommends that in using dose-response information, the influences of various factors should be identified where possible. Pharmacokinetics and pharmacodynamics, the two components of a dose-response curve, are both subject to large interindividual variability. This variability arises from their modulation by factors such as age, gender, co-medications or the presence of concurrent diseases, e.g. renal or hepatic dysfunction. This variability also arises from genetic influences that regulate the expression of drug metabolising enzymes (pharmacokinetic variability) or the function of various pharmacological targets (pharmacodynamic variability). The presence of variant alleles often exerts influences that usually far exceed those due to the other covariates stated above.

It is estimated that the human genome has about 50 000–100 000 functional single nucleotide polymorphisms (SNPs) [variations in the DNA in which a single base pair varies]. These SNPs give rise to variant alleles responsible for genetic polymorphisms within a population and may account for genetically mediated interindividual differences in response to clinically prescribed drugs.[2] The need to study genetically determined biochemical variations that characterise humans was first considered almost a century ago.[3,4]

In terms of genetic influences on drug response, two models exist – high genetic and low environment model versus low genetic and high environment model. For many drugs with a shallow concentration-response curve, genetic factors seem to matter only a little, while for others, genetic differences between individuals account for a very significant fraction of the overall variation in drug response. A typical example of an abnormal response that is almost exclusively genetically determined is the prolonged apnoea that follows administration of suxamethonium chloride (a muscle relaxant) to individuals who inherit a variant form of plasma butyrylcholinesterase (designated atypical cholinesterase). Subsequently polymorphism in the metabolism of isoniazid by *N*-acetyltransferase 2 (NAT2) explained the susceptibility of some individuals to drugs metabolised by acetylation, e.g. peripheral neuropathy, hepatitis or poor anti-tuberculous response following administration of isoniazid or haematological reactions or poor therapeutic response to dapsone. Beginning in the late 1970s, major advances in pharmacogenetics followed the discovery of genetic polymorphism in enzymes that catalyse phase I metabolism (cytochrome P450 [CYP]). This discovery not only explained further the individual susceptibility to drug reactions and lack of efficacy, but also provided a mechanistic and rationale basis for metabolic drug interactions.

At a pharmacokinetic level, use of pharmacogenetics has already resulted in great improvement of cancer therapy with mercaptopurine and azathioprine. These drugs are metabolised by thiopurine S-methyltransferase (TPMT) that is expressed polymorphically in a population. At a pharmacodynamic level, great advances have been made in uncovering the genetic and molecular bases of con-

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