Chirality and drugs used to treat psychiatric disorders

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Numerous psychiatric drugs, particularly antidepressants, have one or more chiral centres (centres of asymmetry) introduced during synthesis; this results in the formation of enantiomers (nonsuperimposable mirror images) which may differ from one another markedly with regard to pharmacodynamic and pharmacokinetic properties.[1] During synthesis, enantiomers are usually produced in equal quantities, and the resultant drug is a racemate (mixture of enantiomers in equal proportions). Separation of enantiomers is often difficult and costly, and in the past, most such drugs have been marketed as racemates, despite the fact that use of single enantiomers may have several advantages.

Enantiomers usually involve one or more carbon atoms that have 4 different groups attached to them.[2] Pairs of enantiomers differ in their optical activity, with one rotating plane polarized light to the right [(+) or *dextrorotatory*] and the other to the left [(–) or *levorotatory*], and the enantiomers are thus prefixed by (+) and (–), *dextro-* and *levo-* or *d-* and *l-*. The terms *R* (*rectus*) or *S* (*sinister*) are used to describe the absolute configuration of enantiomers, and these descriptions are based on the order of the arrangement of the constituents about the chiral centre.[3] There is no relation between absolute configuration and optical activity (e.g., some drugs are *R*(+), *S*(–), whereas others are *R*(–), *S*(+)).[2] The absolute configurations of amino acids and carbohydrates are still designated D- and L-, using D-glyceraldehyde as the standard for comparison, but these designations are based on historical reasons. For a recent helpful review of nomenclature in stereochemistry, readers are referred to the paper by Caldwell and Wainer.[4]

Because drugs often interact with 3-dimensional structures, such as binding sites on metabolizing enzymes, plasma proteins, transporters and receptors, the enantiomers of a drug may differ considerably in their pharmacological activities (the more active enantiomer is termed the eutomer and the less active the distomer) and pharmacokinetic profiles. Thus, administration of racemates often results in far more complex pharmacokinetics than is observed when single enantiomers are administered.

Analytical techniques used to measure body fluid or tissue levels of drugs often do not differentiate enantiomers, despite the fact that the enantiomers may be absorbed, metabolized and excreted at different rates.[1,5] Stereoselective disposition and pharmacodynamics have explained numerous anomalous concentration–effect and drug–drug interaction findings with racemic drugs.[6–18] Such considerations are relevant to physicians, patients, researchers, the pharmaceutical industry and drug regulatory agencies.

Interest in the chirality of drugs has been stimulated in recent years by improvements in methods for the analytical and preparative resolution of racemic drug

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mixtures and the increasing development of drugs designed to interact with targets that can be described in considerable atomic detail.[19] The use of individual enantiomers may simplify dose–response relations, reduce the total drug required, remove a source of intersubject pharmacokinetic and pharmacodynamic variability and minimize toxicity (including effects antagonistic to the therapeutic effect) due to one of the enantiomers.[13,16,18,19]

Although standardized international regulations regarding the use of enantiomers are not yet in place, regulatory guidelines are now present or under development in several countries.[13] Concern about the above matters has led to increased investigation of enantiomers early in drug development and increased "chiral switching" (replacement of a drug that has already been developed or approved as a racemate by a single enantiomer).[13,20] It is interesting in this regard that situations exist where companies originally developing the racemate did not patent the individual enantiomers.[20]

Psychiatric drugs that contain a chiral centre and are currently used as racemates include: the antidepressants trimipramine, fluoxetine, citalopram, tranylcypromine, viloxazine, mianserin, venlafaxine, mirtazapine and reboxetine; the antipsychotics thioridazine (its metabolites mesoridazine and sulforidazine are also marketed) and sulpiride (available in some countries as a racemate and in others as *S*-sulpiride) and the hypnotic drug zopiclone. In several cases, the individual enantiomers differ markedly from one another with regard to pharmacological properties, adverse effects, binding to various receptors and uptake sites, elimination half-lives and interactions with cytochrome P450 (CYP) enzymes.[15,17,21] Although not apparently an important factor with the psychiatric drugs currently available, the possibility that one enantiomer may induce or inhibit the metabolism of another must also be considered.

Amitriptyline does not have a chiral centre, but one is introduced during metabolism. Sertraline and paroxetine have chiral centres, but only one enantiomer is marketed; a similar situation exists with methotrimeprazine. Risperidone does not have a chiral centre, but one is introduced in the formation of 9-hydroxyrisperidone, its major metabolite.

Chiral switching has not occurred extensively with psychiatric drugs, but a recent example involves the selective serotonin reuptake inhibitor (SSRI) citalopram. The racemate was marketed originally, but the *S*-enantiomer (escitalopram), which is the therapeutically active form, is now marketed in the United States[22] and is being considered by regulatory agencies in other countries. Advantages that have been proposed for escitalopram over the racemate include increased potency and the avoidance of adverse effects attributable to the *R*-enantiomer.[23] Studies in animal models and in depressed patients have suggested a relatively rapid onset of escitalopram,[23–27] and it will be of interest to see if this is observed consistently in future clinical practice. Metabolic studies[15] suggest that *S*-citalopram is the preferred substrate for CYP3A4 and CYP2C19, whereas the *R*-enantiomer is the preferred substrate for CYP2D6. Thus, the pharmacokinetics of escitalopram should be less complex relative to the racemate. Patents for the individual enantiomers of the SSRI fluoxetine have been issued; the *R*- and *S*-enantiomers were being developed as an antidepressant and as a treatment for migraine,[20] respectively, although development of the *R*-enantiomer apparently has been suspended.[15] Advantages claimed for *S*-fluoxetine over the racemate include faster onset of action, reduced side effects and increased antidepressant response rate.[15,20,28]

The advances made in recent years with regard to structures of various sites of drug action and improved methods for analyzing and preparing drug enantiomers (which make development of enantiomers more feasible from an economic standpoint) should result in continued interest in the commercial marketing of individual enantiomers. Depending on guidelines issued by regulatory agencies, companies may still decide to develop racemates (e.g., in cases where both enantiomers make an important contribution to the overall therapeutic effect through complementary actions), but such decisions will have to be based on a comprehensive knowledge of the pharmacodynamic and pharmacokinetic properties of the individual enantiomers.

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