Mirror, Mirror on the Wall, Which Enantiomer Is Fairest of Them All?

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Issue: *Numerous psychotropic drugs exist as a mixture of 2 mirror-image stereoisomers of each other, each called an enantiomer and the mixture called a racemate. Often the drug can be improved when only 1 of the enantiomers is administered.*

A flurry of new versions of known drugs is entering psychiatry. These new drugs are made by removing 1 mirror-image stereoisomer from a mixture of 2 contained in the original drug—a strategy that may lead to some improvements over the originals.

The story is perhaps best exemplified by levodopa, developed years ago for the treatment of Parkinson's disease (Table 1). Levodopa, a dopamine precursor, comes in 2 different 3-dimensional forms, but only 1 version is active.[1] Not until the *dextro* form was removed could progress be made in using this agent for Parkinson's disease, because side effects, some quite serious, limited the utility of the racemic mixture.

Several other agents in the fields of psychopharmacology, gastroenterology, allergy, and various therapeutic areas are recognized as racemic mixtures, sometimes called *R* and *S* (or *recto* and *sinister*), sometimes D and L (or *dextro* and *levo*), sometimes + and – (Figure 1). Examples of recent attempts to improve the original drug (Table 1) show that this approach is sometimes but not always successful. Because some selective enantiomers are substantial improvements over racemic mixtures, new drugs are now rarely developed as racemic mixtures. Improvements are illustrated in Figures 2 and 3, and can range from lessened side effects, to reduced drug interactions (Figure 2), to better efficacy including a better relationship between efficacy and a reduced drug dose (Figure 3), to the simple commercial advantage of patent extension.

Table 1. Examples of Racemates and Enantiomers In Psychopharmacology

Original Drug Racemate/ Active Enantiomer	Enantiomer		
	Advantages	Disadvantages	Outcome
D,L-Dopa/ L-Dopa[1]	Dose reduction, improved tolerability	Unknown	Marketed
Fluoxetine/ (R)-Fluoxetine[2]	Improved drug interactions	Cardiotoxicity	Discontinued
Citalopram/ Escitalopram[3]	Dose reduction, lower doses possibly more effective, some side effects lessened, some drug interactions reduced	Unknown	Marketed
Methylphenidate/ Dexmethylphenidate	Dose reduction, possible other advantages	Unknown	Marketed
Zopiclone/ Esopiclone	Possibly improved tolerability	Unknown	Testing in progress
Bupropion/ +-6-Hydroxybupropion	More potency, possibly more efficacy	Unknown	Testing in progress
d,l-Amphetamine/ *d*-Amphetamine[4]	*d*- Isomer may be more advantageous in some patients (releases only dopamine)	Racemate may be more advantageous in some pts. (releases both norepinephrine and dopamine)	Both racemate and *d*- isomer are marketed

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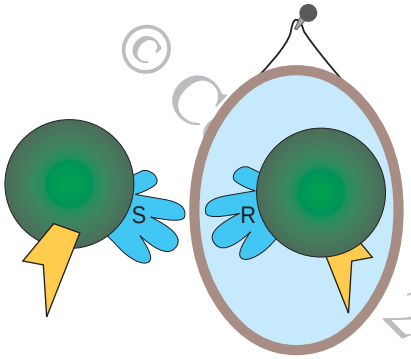
Figure 1. Stereoisomers: Mirror Images[a]

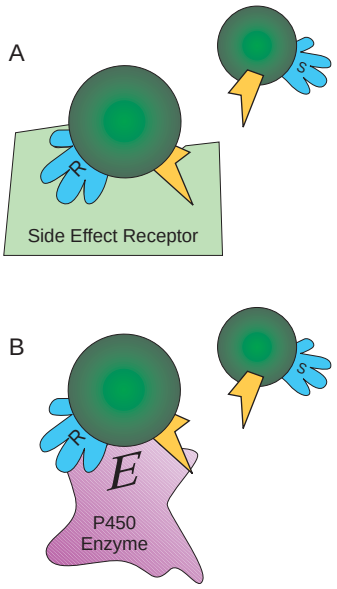


[a]Shown here are 2 mirror-image stereoisomers of a drug, called *R* and *S*.

Take-Home Points

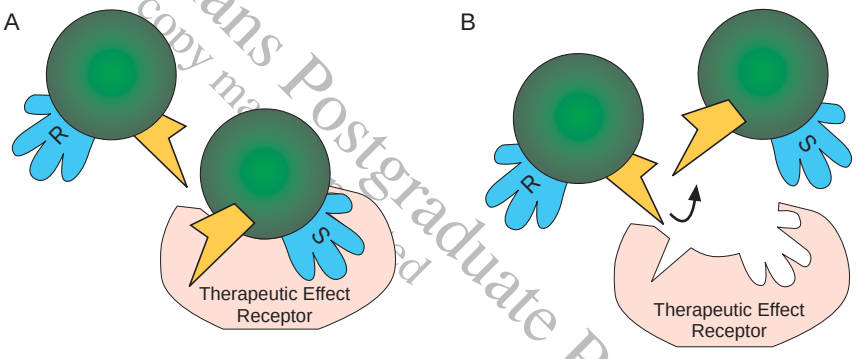
- Drugs that are racemic mixtures may include both a stereochemical version that mediates therapeutic actions and another stereochemical version that mediates side effects or drug interactions.
- Old drugs that exist as racemic mixtures are increasingly being relaunched with the inactive isomer removed.
- Single isomer drugs can be preferable if they allow reduction in dosage, improved therapeutic efficacy, better relationship between dose and therapeutic effects, fewer side effects, and reduced drug interactions.

Figure 2. Side Effects and Drug Interactions Mediated by Selective Binding[a]



[a]In the example shown, only the *R* enantiomer binds to either a neuroreceptor (A), which mediates side effects, or the active site of a P450 enzyme (B), which mediates drug interactions. Thus, removal of the *R* enantiomer from a racemic mixture would eliminate side effects mediated by binding at this receptor or the drug interactions mediated by inhibiting this P450 enzyme.

Figure 3. Interference in a Racemic Mixture[a]



[a]In the example shown, only the *S* enantiomer binds to the receptor that mediates the therapeutic actions of the racemic mixture (A). In some cases, the *R* enantiomer may reduce actions of the *S* enantiomer and thus interfere with its therapeutic actions (B). In such a case, removal of the inactive *R* enantiomer can actually enhance the efficacy of the *S* enantiomer by eliminating this interference. Such may be the case for escitalopram.[3]

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