

Conclusion: The Future of Single-Isomer Pharmacology

By Jerrold F. Rosenbaum, MD

Taken together, the articles gathered in this supplement underscore the major role in drug development that single-isomer science can play—a role that will undoubtedly take on a greater importance in the future. While the chirality of certain pharmacologically active molecules has been recognized for almost a century, it is only in recent years that drug synthesis and chiral separation techniques have advanced far enough to allow meaningful comparisons among enantiomers. Now that these methods are broadly available, the potential applications of single isomer drug development are considerable.

Numerous examples from a range of therapeutic areas confirm that single enantiomers can enhance clinical efficacy, reduce adverse effects, cause fewer interactions with other drugs, and minimize response variations among patients by offering more predictable pharmacokinetics and greater selectivity. In some cases, these advantages are simply due to the removal of an inactive enantiomer, but in other cases, a given dose of a single isomer offers greater benefits when administered alone than when administered as the racemic mixture, suggesting that the opposite enantiomer (the distomer) actually has detracting effects. As the papers by Drs. Gal and Hutt explain, the different activities of a pair of enantiomers are usually traceable to stereochemical differences in the way they interact with chiral macromolecules such as enzymes, transport systems, and receptors.

Drs. Flockhart and Nelson illustrate these principles in their review of esomeprazole in the management of peptic ulcers and levalbuterol in the treatment of allergic asthma. Esomeprazole offers greater bioavailability than its racemate, omeprazole, and hence produces greater and more prolonged suppression of gastric acid secretion. Similarly, many of the adverse effects of racemic albuterol have been traced to the *S*-enantiomer, and removing it from the racemic mixture significantly reduces airway hyperreactivity and the need for rescue medications.

Dr. Gal shows how chiral science is being used today to develop improved treatments for gastrointestinal motility disorders, anxiety, dyslipidemia, bacterial and fungal infections, epilepsy, and cancer. As described by Drs. DeVane and Boulton, these principles are also relevant to the clinical use of antidepressants. Some of the widely prescribed agents in this class exist as racemic mixtures, but adverse effects or drug interactions attributable to one of the enantiomers may hamper their utility. The distomers, for example, may have little or no antidepressant activity, and their presence may complicate pharmacokinetic and pharmacodynamic mechanisms.

These findings are now known to be relevant to escitalopram, the *S*-enantiomer of the selective serotonin reuptake inhibitor citalopram. Escitalopram is the most serotonin-selective compound in its class and is ~30-fold more potent than (*R*)-citalopram. As reviewed by Drs. Owens, Rosenbaum, and Gorman in their respective articles, clinical trials comparing escitalopram (10–20 mg/day) and citalopram (20–40 mg/day) show that both drugs significantly improve symptoms of depression and anxiety relative to placebo, and that overall response rates are higher with both compounds than with placebo. However, escitalopram's actions are clinically apparent after just 1 week of treatment, whereas citalopram does not begin to differ from placebo until 4 to 6 weeks after treatment is initiated. Furthermore, escitalopram is significantly superior to citalopram at several time points, suggesting that it has not only a faster onset of action, but also a greater overall effect than citalopram in controlling depression and associated anxiety.

In summary, the isolation and development of single isomers has advanced the safety and efficacy of a broad range of drugs, and will continue to do so. However, much remains to be learned, and it is clear that not all single isomers will have advantages as predicted by their more specific pharmacodynamic characteristics. For example, sotalol consists of two enantiomers that are both potassium channel antagonists and therefore act as class III antiarrhythmic drugs. One of these enantiomers has β -blocking activity while the other, dexsotalol, has almost none. Dexsotalol was therefore investigated as a possibly superior antiarrhythmic agent. However, it was abandoned because of unexpectedly high cardiac mortality rates, which are now thought to reflect a protective quality of the racemate's β -blockade. This highlights the need for continued basic and clinical research to unravel these complexities and better predict which single enantiomers will yield treatment benefits.

Several single-isomer drugs offer important advantages in enhanced therapeutic efficacy at equal or lower doses, reduced side effects and drug interactions, and clearer relationships between drug concentration and effect. These enhancements offer clinicians the opportunity to treat their patients more safely and effectively, thereby minimizing the personal and financial costs associated with high doses, side effects, and repeat office visits. Single isomers represent a step forward in the search for better, safer, and more cost-effective drugs, and chiral science will play an increasingly important role in future medical advances. **CNS**

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The Biological and Clinical Significance of Single Isomers

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6 Participant Biographies

8 Single-Isomer Science: The Phenomenon and Its Terminology

By Joseph Gal, PhD

14 The Development of Single-Isomer Molecules: Why and How

By Andrew J. Hutt, PhD

**23 Single Isomer Versus Racemate: Is There a Difference?
Clinical Comparisons in Allergy and Gastroenterology**

By David A. Flockhart, MD, PhD, and Harold S. Nelson, MD

28 Great Expectations in Stereochemistry: Focus on Antidepressants

By C. Lindsay DeVane, PharmD, and David W. Boulton, PhD

34 Escitalopram: A Second-Generation SSRI

By Michael J. Owens, PhD, and Jerrold F. Rosenbaum, MD

**40 Efficacy Comparison of Escitalopram and Citalopram in the Treatment
of Major Depressive Disorder: Pooled Analysis of Placebo-Controlled Trials**

By Jack M. Gorman, MD, Andrew Korotzer, PhD, and Guojin Su, PhD

45 New Single-Isomer Compounds on the Horizon

By Joseph Gal, PhD

55 Conclusion: The Future of Single-Isomer Pharmacology

By Jerrold F. Rosenbaum, MD



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