Association of Physicians of India: Position Statement on Role of Chirally Pure Molecules in Clinical Practice

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Abstract
Chirally pure molecules or enantiomers are non-superimposable mirror images of each other with a chiral center (such as carbon, sulphur, nitrogen or phosphorous atom). An equimolar mixture of enantiomers forms a racemate. Chirally pure molecules (single enantiomers) are important in the field of drug discovery as the drug targets such as enzymes and receptors are enantioselective in nature. Clinical studies have demonstrated that chirally pure drugs exhibit different pharmacokinetic and metabolic profiles, reduced adverse events, improved safety profiles and similar therapeutic activity at lowered drug dosage as compared with the racemate in many therapeutic areas. However, since there is a low level of awareness on the advantages of chirally pure molecules among clinicians, pharmacists and patients in India, the Association of Physicians of India (API) developed this position statement to increase awareness on the concept of chirality and the associated advantages of using chirally pure drugs in certain therapeutic areas to maximize patient outcomes. This includes the clinical evidence associated with single enantiomers such as S-metoprolol, S-amlodipine, esomeprazole, escitalopram, levobupivacaine, cisatracurium, S-etodolac, dexketoprofen, levofloxacin in terms of efficacy and safety as compared with their racemates. In addition, the API also provides some tactical recommendations for clinicians, pharmacists, patients, regulatory body and pharmaceutical companies to increase awareness on chirally pure drugs and puts forth the need for expedited availability of chirally pure drugs in the Indian market.

Introduction
Chirality has gained considerable attention in pharmaceutical drug development as there is a greater understanding on the implications of single-enantiomers in improving drug therapeutic profile.¹ The global trend towards development of single enantiomers as new drugs for various diseases started in the late 1980s and chiral molecules comprised almost half the marketed drugs by 2000.¹ Between January 2010 to November 2014, 127 new molecular entities (NMEs) were approved by the United States Food and Drug

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Administration (US FDA) of which 81 (64%) were chiral drugs with single enantiomers as a majority. Thus there is a trend towards the development of single enantiomers over racemic mixtures in drug development. Chiral drugs are also available in India but there is a need for generating awareness among clinicians (including academicians and researchers), pharmacists and patients about the potential benefits of chirally pure drugs.

The word ‘chiral’ is derived from the Greek word ‘cheir’ which stands for ‘hand’ or handedness (Figure 1). Chiral molecules or enantiomers can be compared to the right and left hand i.e. the molecules cannot be superimposed on each other and comprise a chiral center (e.g., carbon, sulphur, nitrogen or phosphorous atom). Isomers are the molecules with similar molecular formula but different chemical structure. They are further classified into stereoisomers that differ in the spatial or three-dimensional arrangement of atoms. Configurational isomers are stereoisomers that cannot be converted to one another by rotation around a single bond. Enantiomers are configurational isomers that are non-superimposable mirror images of one another. Based on the standard nomenclature used, enantiomers are classified as rectus (R) or sinister (S) based on atomic mass and number (Figure 2). A racemate is an optically inactive, equimolar mixture of two enantiomers and at times could have different properties than either of the pure enantiomers. Chirality is an integral part of nature, such as some naturally occurring flavonoids like pisatin, medicarpin, vestiton. Similarly, in biological systems, amino acids, carbohydrates, nucleosides, proteins, enzymes, and hormones are chiral compounds. Receptors and enzymes are proteins (composed of amino acids), that bind their ligands in an enantioselective manner. Hence, in designing
molecules for drug targets such as proteins or enzymes, chirality is increasingly important.

The concept of chiral separation was first introduced by Louis Pasteur in 1848, in separating enantiomers of sodium ammonium tartrate. Since then, chiral technology has made tremendous progress with advances in the synthesis, separation, and analysis of pure enantiomers from racemates. Chiral drug development includes development of a single enantiomer or switching over to a single enantiomer from an already existing racemate or the development of a fixed ratio of enantiomers. Single enantiomers or chirally pure drugs exhibit different pharmacological activity and metabolism as compared to the other enantiomer in the racemate. They may provide advantages of similar efficacy at lower doses, improve safety and reduce the metabolic load if therapeutic activity is associated with one enantiomer.

The importance of chirality was evident in the thalidomide tragedy. Thalidomide, an anti-emetic prescribed for morning sickness in pregnant women, was a racemic mixture wherein the active R-enantiomer was associated with efficacy and the S-enantiomer was responsible for teratogenicity. The racemate led to phocomelia (failure of limb development) in infants thus resulting in its withdrawal. This tragedy (1961-1962) made scientists reflect on the significance of single enantiomers in drug development.

Chiral drugs are available in India and with the aim to increase awareness on these drugs among clinicians (including academicians and researchers), pharmacists and patients, a panel meeting was held under the aegis of the Association of Physicians of India (API) to discuss chirally pure drugs in different therapeutic areas and the regulatory considerations followed by other countries on chiral drugs (2nd July, 2017, Mumbai). The panel of 23 members comprised of anesthesiologist, cardiologists, endocrinologists, orthopedician, nephrologist, pharmacologists, physicians, pulmonologist, psychiatrist, and rheumatologist practicing in different regions across India. The discussion was based on chiral drug development and associated challenges, the regulatory considerations for chiral drugs in different countries and the advantages of some of the chirally pure drugs in the therapeutic areas based on the clinical expertise of the panelists. This position statement provides recommendations on generating awareness on the potential benefits of chirally pure drugs among regulatory bodies, pharmaceutical companies, clinicians, pharmacists, and patients. This position statement puts forth the need for expedited availability of these drugs in the Indian market.

**Chiral Switching and Advantages of Chirally Pure Drugs**

Chiral or racemic switching is the development of single enantiomers from previously approved and marketed racemic mixtures or mixtures of diastereomers. Single enantiomers developed from the racemate, have different qualitative and quantitative, pharmacodynamic and pharmacokinetic properties. A large number of “old” racemic mixtures have been re-examined for their potential to be developed as single enantiomers with more selective and enhanced therapeutic profiles (Figure 3) and possibly for newer indications. However for many racemic drugs the stereospecificity is yet to be evaluated.

Levocetirizine, a single-enantiomer of cetirizine (racemate), is an anti-histamine used in the alleviation of allergy symptoms. It demonstrates higher H1 receptor affinity, is stereoisomerically stable in vivo, and has low renal clearance as compared with dextrocetirizine. Less sedation has been reported with levocetirizine leading to a better side effect profile as compared with cetirizine, consequently advancing its use in therapy. Thus single enantiomers may also display reduced adverse effects in comparison to racemic mixtures.

An active enantiomer may also demonstrate similar therapeutic activity with better safety profiles
at lowered drug dosage. Ibuprofen, a non-steroidal anti-inflammatory drug, is commonly prescribed as an analgesic and antipyretic in adults and children.\textsuperscript{19,20} Dexibuprofen, the S-enantiomer of ibuprofen, has demonstrated similar efficacy at half the dose of ibuprofen. Its potential advantages include less toxicity, lowered variability in therapeutic effects as well as reduced renal and metabolic load on the body. Additionally, dexibuprofen does not demonstrate cardiac toxicity associated with R-enantiomer thus providing an improved safety profile.\textsuperscript{21-23}

Additional advantage of chirally pure drugs include lowered drug-drug interactions.\textsuperscript{22,24} A stereoselective interaction was observed between metronidazole and S-warfarin; wherein metronidazole inhibits cytochrome P450 2C9 isozyme (CYP2C9) that is primarily responsible for the metabolism of S-warfarin.\textsuperscript{25-27} Interactions between warfarin and metronidazole can be prevented by using R-warfarin instead of the commonly used racemic mixture. Enantiomers also exhibit different pharmacological mechanism of action and therefore can be used potentially for different therapeutic indications. For e.g., quinine has antimalarial activity while quinidine (stereoisomer of quinine) has an anti-arrhythmic property, levomethorphan is a potent opioid analgesic while dextromethorphan is an antitussive.\textsuperscript{28,29}

Single enantiomers of a chiral drug often demonstrate discrete differences in their pharmacokinetic and metabolic profiles both quantitatively and qualitatively. Thus prospective discrimination between the metabolites of enantiomers at each pharmacokinetic stage is easier with single enantiomers (Figure 4).\textsuperscript{7,11}

**Figure 4: Advantages of chirally pure drugs**

Development of Chirally Pure Drugs and Associated Challenges

Single enantiomers are purified from racemic mixtures by utilizing classical resolution techniques or other modern technologies. Classical resolutions utilize acid-base reactions leading to separation of the single enantiomers from the mixture. Further separation is carried out by crystallization of the two salts, by filtration of the soluble salt from the insoluble one or by liquid chromatography. Kinetic resolution utilizing biological catalysts (e.g., yeasts, molds, bacteria) to degrade one enantiomer and hence separate the other that remains in solution is another classical method for chiral separation.\textsuperscript{30}

Commonly used modern technologies for chiral separation include high performance liquid chromatography (HPLC) with chiral stationary phases that directly separate the single enantiomers. Simulated moving bed chromatography and chiral catalysts are also utilized for chiral separation. For clinical chemical analysis of biosamples, HPLC and gas chromatography are used. For bioanalysis of the chiral drug, HPLC, gas chromatography, supercritical fluid chromatography, and capillary electrophoresis are performed. Chiral immunoassays can also be performed to analyze the quantity of single enantiomer from biological samples.\textsuperscript{3} Challenges associated with development of single enantiomers include development and standardization of processes for separation and characterization of single enantiomers, scale-up of a synthetic route of separation for the continuous production of the single enantiomer, requirement of pure enantiomer and racemate to initiate the process, and development of sensitive and specific analytical assays to differentiate enantiomers from racemic mixtures throughout the preclinical, clinical, and production cycle of the drug.\textsuperscript{8}

**Regulatory Considerations for Developing Chirally Pure Drugs**

United States Food and Drug Administration guidelines

The US FDA published their policy on the development of new stereoisomeric or chirally pure drugs in 1992 (Table 1).\textsuperscript{31} This policy focusses on some general as well as specific issues including chemistry, methodology and specification on drugs, pharmacology, pharmacokinetics, toxicology and the permissible impurity limits in relation to chirally pure drugs. The policy requires that for all chiral drugs, the quantitative isomeric composition of the material be identified early on in the drug development process and the information specified during the drug approval process.
Table 1: Regulatory guidelines on single enantiomer drug development

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<tr>
<td>Focuses on chemistry, methodology and specification of drugs, pharmacology, pharmacokinetics, toxicology of single enantiomers</td>
<td>Single enantiomer from racemate will be a new application</td>
<td>Enantioselective determination of drug substance utilizing chiral assays and controlling for enantiomeric impurities</td>
<td>Enantioselective tests to be performed for identification and purity of single enantiomer</td>
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<td>Stereospecific activity to be identified in early drug development utilizing stereospecific identity or a stereochemically selective assay method</td>
<td>Reproductive toxicity studies to include pre and post-natal treatment effects from conception</td>
<td>Chirally pure drug to comprise limited amount of second enantiomer (considered an impurity)</td>
<td>Enantiomer stability in vivo and also in stability studies for the shelf life testing of the drug</td>
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<td>For switching to single enantiomer, bridging studies are to be conducted that include the longest repeat-dose toxicity studies and reproductive toxicity studies</td>
<td>Bioinversion to be considered</td>
<td>Chiral specific assays for safety and efficacy studies</td>
<td>Metabolism of enantiomer to be followed enantioselectively from pre-clinical studies to phase 1.</td>
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<td>Rationale for developing single enantiomer must be clarified in the drug approval application</td>
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The FDA may guide the sponsors on developing a single enantiomer or the racemate. Although, the final decision lies with the sponsor company, the rationale for developing either enantiomer or racemate must be clarified in the drug approval application.31

**European Medicines Agency Guidelines**

The European Medicines Agency (EMA) guidelines (1994)32 in addition to the FDA guidelines recommend that a single enantiomer drug developed from an approved racemic mixture would be considered as a new application, wherein the rationale behind the development should be mentioned (Table 1). The enantiomeric purity of the single enantiomer should be defined and the possibility of inversion in vivo should be considered.

**International Conference on Harmonization of Technical Requirements Guidelines 6QA**

The International Conference on Harmonization (ICH) of Technical Requirements guidelines (1999) 6QA for the ‘Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances’ is followed by many countries (Table 1).33 These guidelines like the others, recommend enantioselective determination of drug substance utilizing chiral assays and controlling for enantiomeric impurities. The efficacy and safety must be analyzed by a chiral assay that is able to distinguish between the two isomers.

**Health Canada guidelines**

The Health Canada guidelines (2000)34 also lets the sponsor decide whether a racemic mixture or single enantiomer is to be developed but recommends that the decision be driven by safety, efficacy, quality and risk-benefit assessment data. The recommendations are similar to those proposed by the FDA (Table 1).

**Regulatory Considerations followed by India**

The Central Drug Standard Control Organization (CDSCO) of India has published a “Guidance for the industry on the preparation of common technical document for import/manufacture and marketing approval of new drugs for human use” that is based on the ICH Harmonised Tripartite Guideline on “Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use” M4, Step 4 (2004).33,35 India follows these guidelines for the approval of new drugs. For chiral drugs, the guideline recommends that the specific stereoisomer be mentioned in the characterization of drug and also if the final product intended for marketing is the same stereoisomer that has been investigated in the non-clinical and clinical studies. Additionally, if the molecule is a racemate or a single enantiomer then the implications of any difference between the compound investigated and intended for marketing should be clarified in the documents.35 There are no special guidelines recommending the drug approval processes of chirally pure drugs in India.

In India, the registration pattern for approval of single enantiomers (with efficacy and safety established in other countries) is similar to that of new drugs. All the studies done for new drugs in the Indian subpopulation are also required for chiral drug approval in India even though they have been approved by other countries. Since the Indian regulatory requirements for chirally pure drugs are extensive, there may be a delay in their availability to Indian patients.

**Therapeutic Areas Currently Employing Chirally Pure Drugs**

Chirally pure drugs are prescribed as therapy in the areas of cardiology, gastroenterology, neuropsychiatry, rheumatology, etc. (Table 2). Some of them are briefly discussed below as a part of this review.
Table 2: Commonly utilized chirally pure drugs

<table>
<thead>
<tr>
<th>Cardiology</th>
<th>Gastroenterology</th>
<th>Neuropsychiatry</th>
<th>Endocrinology</th>
<th>Anaesthesia</th>
<th>Rheumatology, pain and inflammation</th>
<th>Pulmonology</th>
<th>Infectious diseases</th>
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<tr>
<td>Anti-anginal</td>
<td>Esomeprazole</td>
<td>Anti-convulsants/</td>
<td>Levothyroxine</td>
<td>S-etomidate</td>
<td>S-penicillamine</td>
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<td>Hypnotics</td>
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<td>S-amlodipine</td>
<td>S-pantoprazole</td>
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<td>S-fluoxetine</td>
<td>S-ketamine</td>
<td>S-etodolac</td>
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<td>Antihypertensive</td>
<td>Dexrabeprazole</td>
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<td>S-zopiclone</td>
<td>Levobupivacaine</td>
<td>Dexketoprofen [S-ketoprofen]</td>
<td>Levocetizine</td>
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<td></td>
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<td>Anti-Parkinson</td>
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<td>R-formoterol</td>
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<td>S-metoprolol</td>
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<td>Ropivacaine</td>
<td>Dexibuprofen [S-ibuprofen]</td>
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<td>S-atenolol</td>
<td>Levodopa</td>
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<td>S-amlodipine</td>
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<td>Escitalopram</td>
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**Cardiology**

Hypertension, a risk factor for stroke and other cardiovascular diseases, is treated with beta-blockers, some of which exist as R- and S-enantiomers having different pharmacokinetic and pharmacodynamics properties.36-38

The S-enantiomer of metoprolol possesses higher affinity towards the β1 receptor as compared with the R-enantiomer (S:R=33:1, beta blocking activity), hence S-metoprolol may be preferred in the treatment of hypertension.38

In a double-blind, randomized clinical trial, S-metoprolol (50 mg, extended-release [ER]) demonstrated a 13.6% increase in responders (>20 mm Hg reduction in systolic blood pressure or reduction of >10 mm Hg in diastolic blood pressure) on day 21 as compared with racemic metoprolol (100 mg) with comparable safety.39

Similarly, in another prospective trial, S-metoprolol (25 mg and 50 mg ER) was well tolerated with a responder rate of 80% (on day 28) in the treatment of hypertension.40 An open-label, prospective, comparative study reported that the response rate was higher with S-metoprolol (74%, 50 mg ER) as compared with metoprolol (61%, 100 mg ER) in hypertensive patients with angina. There was no significant difference in frequency and severity of adverse events between groups.41 Another open-label, prospective, non-comparative study reported that the S-metoprolol succinate (6.25-50 mg, ER tablet) was effective in reducing the blood pressure, heart rate and improving symptoms in hypertensive patients with congestive heart failure (CHF). The side effects were fatigue and dyspnea, which were mild in nature.42 Another similar study reported that S-metoprolol succinate (50 mg, ER) was safe and effective in the treatment of hypertension in patients with chronic obstructive pulmonary disease.43 S-metoprolol was also efficacious in reducing blood pressure in Indian patients with co-existing illnesses such as chronic obstructive pulmonary disease, angina, angina co-existent with diabetes mellitus, and CHF without major safety concerns.44

A phase 3, multicenter, randomized study in Korean patients with mild to moderate hypertension demonstrated a response rate of 92.7% for blood pressure reduction with S-amlodipine (2.5 mg, a long acting L-type calcium channel blocker) as compared to 88% responders with amlodipine besylate (5 mg). Thus S-amlodipine was therapeutically equivalent and non-inferior to amlodipine besylate.45 Similar results were reported in Indian hypertensive patients.46 A prospective study in Indian hypertensive patients using S-amlodipine (2.5-5 mg) therapy reported low incidence of pedal edema (0.75%) which is a common side-effect of calcium channel blockers.47 In a post marketing study (n=1076), pedal edema was reported in 51% (300/589) patients using amlodipine. Upon initiation of S-amlodipine (2.5 mg or 5 mg), edema resolved in 95.67% (287/300) patients. Post 30 days of therapy, edema was observed in 1.77% patients compared to 31.88% before therapy (p<0.0001).48 S-atenolol (25 mg) has demonstrated efficacy similar to atenolol (50 mg) in patients with hypertension.49 Thus, the S-enantiomers of metoprolol, amlodipine and atenolol demonstrated similar efficacy at half the dose of the racemate and they are currently marketed in India.38

**Gastroenterology**

Diseases such as gastroesophageal reflux disease (GERD), Barrett’s esophagus, Zollinger-Ellison syndrome and peptic ulcers are treated using proton-pump inhibitors (PPIs) that block H, K-ATPase thereby inhibit gastric acid secretion.50 The PPIs belong to the class of substituted benzimidazoles with a chiral sulphur. S-omeprazole (also known as esomeprazole), was the first chirally pure PPI which was developed due to its higher metabolic stability (chiral stability i.e. resistant to inversion, as observed in humans). It has higher bioavailability and less inter-patient variability as compared to omeprazole in clinical studies.51,52

A systematic analysis has demonstrated a significantly higher odds of maintaining the gastric pH >4 with esomeprazole as compared with omeprazole (odds
In three studies, 53,54,55 S-omeprazole also demonstrated superiority as compared to omeprazole in the treatment of GERD (odds ratio=1.18; CI=1.01,1.38; p=0.04).55 Since 3% of Caucasians and 15% of the Asian population are poor metabolizers of the P450 cytochrome system, the metabolites of the racemic mixture are intrinsically cleared three times slower as compared to the chirally pure esomeprazole. This is the primary cause for the plasma concentration variability of the racemic mixture in patients but is advantageous for esomeprazole as it eliminates the need for dose adjustment in patients with mild-moderately severe hepatic impairment.54

In a multi-center, double-blind, randomized study, 56 S-pantoprazole (20 mg) demonstrated efficacy and safety similar to that of pantoprazole (40 mg) at half the dose, in patients with GERD.55 In another study conducted in patients from India with GERD, on day 28, S-pantoprazole (20 mg) therapy led to improvement in symptoms of acid regurgitation (relative risk reduction [RRR] 13%), heart burn (RRR 15%) and bloating (RRR 13%) as compared with pantoprazole.56 Additionally, S-pantoprazole also demonstrated efficacy in GERD patients with or without predominant nocturnal symptoms and peptic ulcer patients (gastric ulcer/duodenal ulcer).57 Similarly, dexrabeprazole (10 mg, the S-enantiomer of rabeprazole), led to lower incidences of regurgitation, residual esophagitis and improved healing as compared with the racemate rabeprazole (20 mg) in patients with GERD.58

**Neuropsychiatry**

Citalopram, a selective serotonin reuptake inhibitor, is commonly used in psychiatric practice for the treatment of major depressive and anxiety disorders. Escitalopram, S-enantiomer of citalopram, is 30 times more potent as compared to the R-enantiomer (also counteracts the activity of the S-enantiomer).59 An expert opinion article reviewing data from multiple clinical trials reported that escitalopram has demonstrated evidence of efficacy as early as 2 weeks, reduced risk of relapse over 36 weeks and reduced symptoms of depression.60 Escitalopram has reduced affinity for post-synaptic receptors, which reduces the possibility of adverse events associated with other psychotropic molecules.60 A pooled analysis comparing escitalopram with citalopram demonstrated higher number of responders with escitalopram at different time points.61 A meta-analysis of randomized clinical trials demonstrated better response (odds ratio=1.44, 95% CI=1.18; 1.75, p=0.0003) and remission (odds ratio=1.86, 95% CI=1.46; 2.36, p<0.0001) with escitalopram as compared with citalopram.62 Additionally, the QTc interval prolongation of escitalopram was half (4.5 ms at 10 mg) as compared with citalopram (8.5 ms at 20 mg).63

S-fluoxetine, an enantiomer of fluoxetine (racemate) used as an anti-depressant, demonstrated a rapid onset of action, higher efficacy and lower rate of adverse events in a phase 2 trial for migraine as compared with the racemate.64 R-fluoxetine reported significant prolongation of cardiac repolarization at higher doses.65 S-zopiclone, a sedative hypnotic has demonstrated efficacy in the treatment of primary chronic insomnia, with no added requirement of dose adjustment in patients with renal failure.66 The anxiolytic effect of S-zopiclone was not associated with substantial central nervous system depression as reported for the racemate zopiclone.67 The racemate 3,4-dihydroxyphenylalanine (Dopa) was replaced by levodopa, the L-enantiomer, due to side-effects such as granulocytopenia.68 Oxazepam, an anxiolytic, is a racemic mixture with rapid interconversion amongst the two enantiomers that is faster than the time required for onset of drug action at ambient temperature. Separation of the enantiomers is not possible as oxazepam presents a unique case of a rapidly interconverting chiral molecule.69

**Endocrinology**

Levothyroxine (an enantiomer of thyroxine) is commonly prescribed for the treatment of hypothyroidism. A dose of 150 µg of levothyroxine is equipotent to 4000 µg of dextrothyroxine in reducing serum thyroid stimulating hormone, triglycerides, cholesterol, and phospholipid levels in hypothyroid patients.70

**Polycystic ovary syndrome (PCOS)** is commonly reported cause of infertility in women of reproductive age. Insulin resistance is one of the common reasons for abnormal ovarian function.71 Myo-inositol (MI) and D-chiroinositol (DCI) (both isomers of inositol), used as insulin sensitizers, demonstrated beneficial effects at metabolic, hormonal, and ovarian level as therapy for PCOS.72,73 The most abundant natural isoform of inositol is MI whereas DCI is formed by epimerization of MI to DCI. Both isomers exhibit different functions i.e. MI improves ovarian function and DCI reduces hyperinsulinemia.72,73 Thus, the combined administration of MI with DCI synergistically aids in correcting hormonal and metabolic imbalance in PCOS patients.74

**Anesthesia**

Etomidate, a short-acting anesthetic drug induces sedation by modulating the gamma amino butyric acid (GABA) receptors. It contains a single chiral carbon atom and studies have established that the R-etomidate has 10 to 20 fold greater potency as compared with S-etomidate thus leading to R-etomidate being developed as a single enantiomer anesthetic.75 S-ketamine, the S-enantiomer of ketamine demonstrated higher...
efficacy as an anesthetic and analgesic as compared with the racemate and also produces fewer psychomimetic adverse effects as compared with R-ketamine and the racemate.76 Hence, S-ketamine is emerging as a potential replacement for ketamine as an analgesic.77

Bupivacaine, a local anesthetic agent has demonstrated cardiotoxic effects and levobupivacaine, the S-enantiomer, has been developed as a safer alternative. Despite higher concentrations of levobupivacaine reported in plasma, it has less effect on mean stroke index. The cardiac arrhythmias induced by bupivacaine may be a result of the R-enantiomer interacting more potently with the sodium channels. Levobupivacaine displays lower potency in inhibiting the sodium channels thus leading to lower cardiotoxicity.78 Ropivacaine is the pure S-enantiomer of propivacaine and is used as a regional anesthetic in surgeries and has displayed lower incidence of motor block, reduced CNS toxicity and reduced cardiotoxicity as compared with bupivacaine.79 Cisatracurium, an R-enantiomer of atracurium, also demonstrated higher potency and lowered release of histamine and laudanosine (an epileptogenic compound) as compared to atracurium and hence is preferred in therapy.80

Rheumatology, Pain and Inflammation

Penicillamine (racemic mixture) and R-penicillamine have demonstrated optic neuritis as an associated adverse event. However, this adverse event does not occur with S-penicillamine use, hence it is preferred for the treatment of rheumatoid arthritis. The toxicity of R-penicillamine may be due to its ability to utilize pyridoxine in some enzymatic reactions leading to its incorporation into the proteins. In contrast, due to its isomeric form, S-penicillamine cannot undergo reactions thus avoiding its incorporation in proteins.81 Etodolac, an anti-inflammatory and analgesic, is a cyclooxygenase-2 inhibitor that is used in the management of rheumatoid arthritis and osteoarthritis.82 S-etodolac (S-enantiomer of etodolac) demonstrated 2.6 times more potency as compared with the racemate mixture.83 S-etodolac at 300 mg demonstrated bioequivalence to etodolac at 600 mg.83,84 A double-blind, randomized, comparative study reported that the S-etodolac (300 mg, ER tablet) was equally effective in the treatment of osteoarthritis in Indian patients in comparison to etodolac (600 mg, ER tablet). Few adverse events were reported and none of them were serious adverse events.85

Dexketoprofen, an analgesic commonly prescribed for relief from post-surgical dental pain and dysmenorrhea, is the S-enantiomer of ketoprofen. A double-blind, randomized, clinical trial demonstrated that dexketoprofen (25 mg) had a faster onset of action and efficacy similar to ketoprofen (50 mg) at half the dose and hence may be used in the treatment of postsurgical dental pain.86 Dexketoprofen (25 mg) also resulted in similar efficacy, safety and tolerability in women with primary dysmenorrhea when compared with twice the dose of ketoprofen (50 mg).87

Pulmonology

Salbutamol (also known as albuterol), a short-acting β2 adrenergic receptor agonist, is a commonly prescribed bronchodilator for relief in the symptoms of asthma and chronic obstructive pulmonary disease.88 Its enantiomers are stereoselective at the β2-receptor with a 68-fold greater potency for R-salbutamol.89 The R-enantiomer metabolizes 12 times faster, leading to higher concentrations of S-salbutamol in the body.90 Since, S-salbutamol is eliminated slowly from the body, it indirectly antagonizes the benefits of R-salbutamol.91,92 Symptom control is achieved by the R-enantiomer at lower doses, thus reducing metabolic load and hence may be preferred in therapy as compared with the racemate.90,91

One of the active metabolites of terfenadine is fexofenadine and is used preferentially in the treatment of rhinitis and urticaria since it has reduced cardiotoxic and sedative effects.93,94 The concentration of S-fexofenadine in human plasma was reported to be higher than R-fexofenadine. It was also observed that R-fexofenadine is metabolized via efflux transporters such as P-glycoprotein, that may be chirally selective and not by the usual CYP450 metabolism pathway. Thus, R-fexofenadine may probably have the advantage of lowered drug-drug interactions and also predictable efficacy as compared with the S-enantiomer.95

R-formoterol, the enantiomer of formoterol administered as a nebulizer (exhibited two fold higher affinity for the β2-receptor) has demonstrated efficacy as a bronchodilator in chronic obstructive pulmonary disease.96,97 Levocetirizine, an antihistamine, is also preferentially prescribed over the racemate cetirizine as it has demonstrated lesser side effects such as sedation.98

Infectious Diseases

Ofloxacin, a quinolone derivative, is a specific inhibitor of DNA gyrase and possesses a broad spectrum antibiotic activity against both gram positive and gram negative bacteria.99 Levofloxacin, the S-enantiomer of ofloxacin is the active enantiomer with the anti-bacterial activity. In a randomized, double-blind clinical trial of patients with complicated urinary tract infections, levofloxacin (300 mg) exhibited anti-bacterial activity and safety comparable to that of ofloxacin (600 mg).100 Levofloxacin (0.5%) also demonstrated superior microbial eradication rates as compared to ofloxacin (0.3%) in patients with bacterial conjunctivitis.101 In addition, in a multidrug regimen used for the treatment of multidrug-resistant tuberculosis, levofloxacin
also reported higher efficacy as compared with ofloxacin. Thus, levofloxacin established an improved safety and efficacy profile compared with ofloxacin.

**Chirally Pure Drugs: Recommendations for India**

The exposure of patients to multiple concomitant drugs has increased due to various co-existing diseases. Hence, it is important that in addition to safety and efficacy, the metabolic load due to the drugs be given due consideration. Reduction in metabolic load may be achieved with the use of chirally pure drugs in place of racemates. The advantages of utilizing chirally pure drugs in certain therapeutic areas as compared with racemic mixtures is also evident from various clinical trials. However, to bridge the gap in awareness on the therapeutic uses of chirally pure drugs, an expert panel delineated issues requiring focus for all the stakeholders (including regulatory body, pharmaceutical companies, clinicians, pharmacists, patients) and outlined certain recommendations (Table 3). There was a unanimous consensus in the panel on the importance of educating the clinicians, pharmacists, and patients regarding the efficacy, safety profile, and benefits of using chirally pure molecules.

**Table 3** Chiral drugs - recommendations for India

<table>
<thead>
<tr>
<th>Stakeholders</th>
<th>Regulatory body</th>
<th>Pharmaceutical companies</th>
<th>Clinicians</th>
<th>Pharmacists</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issues to focus on</td>
<td>Awareness on different policies in different countries for chiral drugs</td>
<td>Making chiral drugs available in the market</td>
<td>Understanding the principle of chirality in drugs</td>
<td>Understanding the difference between racemates and chiral drugs as well as related health-outcomes</td>
<td>Education on the concept of ‘chirally pure drugs’</td>
</tr>
<tr>
<td>Recommendations to resolve issues</td>
<td>Expedited approval process to be considered for chiral drugs basis clinical evidence</td>
<td>Knowledge on efficacy, safety and potency of chiral drugs in clinical practice</td>
<td>To abide by the concerned regulatory requirements for the discovery and development of chirally pure drugs whenever possible.</td>
<td>Awareness on the perils of drug substitution</td>
<td>Awareness on safety and efficacy of chiral drugs</td>
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<td></td>
<td>To conduct round table meeting or panel discussions with regulatory board for framing expedited approval guidelines for chiral drugs</td>
<td>To create awareness via continued medical education or concept based panels to discuss the benefits of chiral drugs over racemates</td>
<td>To conduct policy campaigns on ‘no substitution on prescription’ for pharmacists</td>
<td>To utilize mass media for conducting campaigns such as advertisements relating chiral drugs mentioning safety and efficacy benefits. This could be achieved via health slogans (e.g. ‘purity counts’), storylines with messages, advertisement boards</td>
<td></td>
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<tr>
<td></td>
<td>To update the decision makers (government representatives, health ministry, state bodies and DCGI) on chirality through guideline recommendations and position statements.</td>
<td>To include clinicians in clinical trials for chiral molecules and disseminate the findings of clinical trials for the Indian population to increase awareness among clinicians</td>
<td>To provide counselling services to pharmacists by clinicians to explain the non-equivalence of drugs and prescription sanctity in order to discourage substitution between racemates</td>
<td>To encourage healthcare providers to share their knowledge and experience with patients on using chirally pure drugs</td>
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<td>To provide global perspective by generating awareness on guidelines governing the approval process in different countries so that informed decisions can be made in drafting approval guidelines for chiral drugs</td>
<td>To provide round table meetings, focussed group meetings and position statements would help to educate clinicians on differential benefits of chirally pure molecules</td>
<td>To conduct camps on chirality and chiral drugs to educate pharmacists</td>
<td></td>
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</tbody>
</table>

A larger patient population may be potentially benefitted from available chirally pure drugs if physicians prefer these drugs in their clinical practice. Pharmacists should be advised to adhere to the physician’s prescription and substitution between racemate and chirally pure drugs at the pharmacy level should be strongly discouraged. Patients could be made aware of the potential advantages of chirally pure drugs via physician counselling. Additionally, the regulatory bodies may consider the need to expedite the approval of chirally pure drugs with established efficacy and safety and thus accelerating their availability. Overall, increased awareness on the concept of chirality will translate in to maximum benefits to the patients and optimize the outcomes.
Conclusions

The evidence in certain therapeutic areas clearly demonstrates similar efficacy at lower doses, improved safety, and reduced metabolic load associated with chirally pure molecules in comparison with racemates. However, there is a need for increased awareness on the advantages of chirally pure drugs among clinicians, pharmacists, and patients. Efforts in this direction are warranted for patients to benefit from therapy with chirally pure molecules.

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Author Contributions

All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors provided direction and comments on the manuscript, made the final decision about where to publish the manuscript, and approved submission to the journal.

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