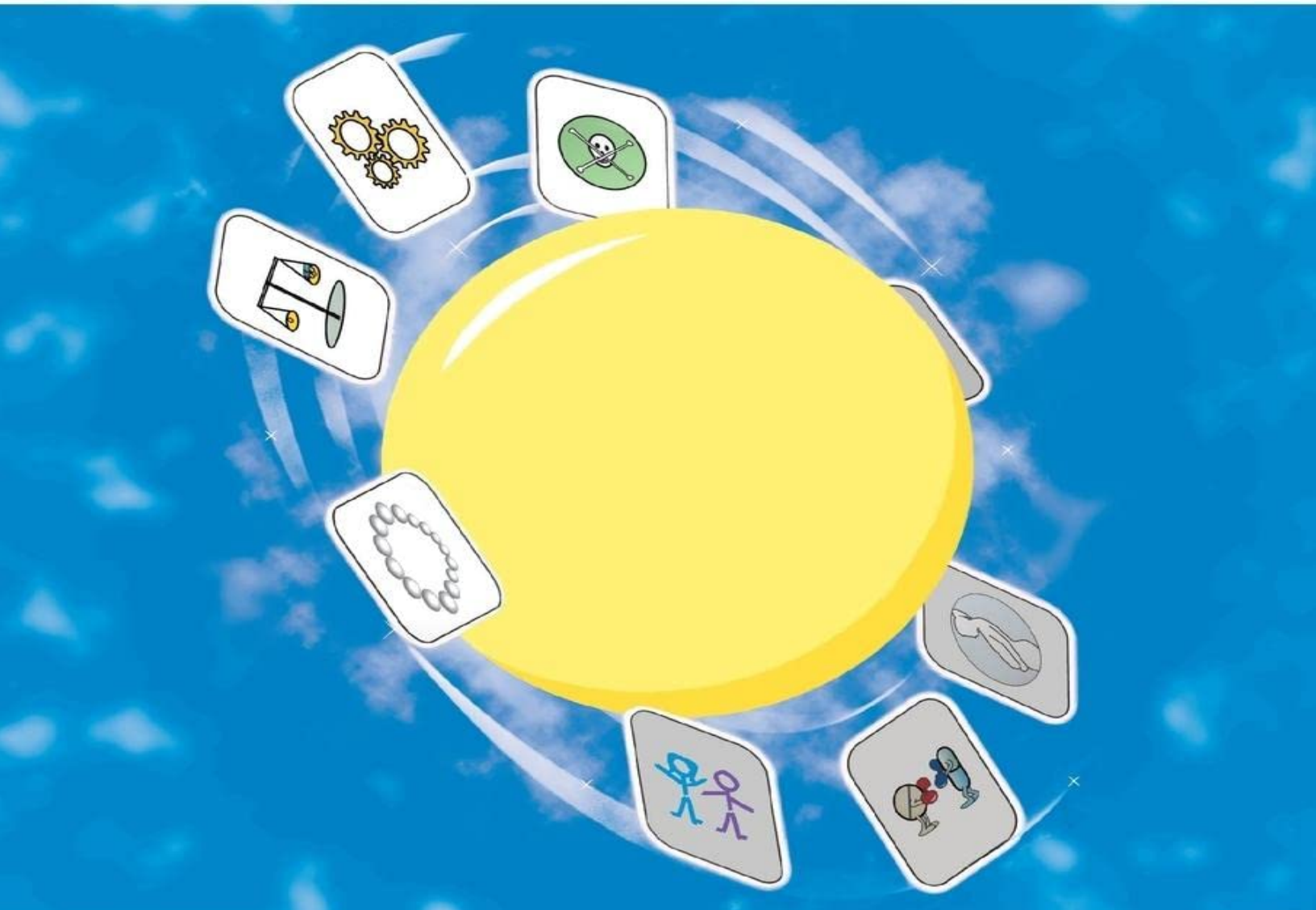
Stahl's

Essential Psychopharmacology

Prescriber's Guide

SEVENTH EDITION

Stephen M. Stahl



CAMBRIDGE Medicine

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY

Prescriber's Guide

SEVENTH EDITION

With the range of psychotropic drugs expanding and the usages of existing medications diversifying, we are pleased to present this very latest edition of what has become the indispensable formulary in psychopharmacology.

This new edition features several new compounds as well as information about new formulations, new indications, and new warnings for existing drugs.

With its easy-to-use, template-driven navigation system, the *Prescriber's Guide* combines evidence-based data with clinically informed advice to support everyone prescribing in the field of mental health.

Stephen M. Stahl is Professor of Psychiatry and Neuroscience at the University of California, Riverside and San Diego and Honorary Visiting Senior Fellow in Psychiatry at the University of Cambridge, UK. He has conducted various research projects awarded by the National Institute of Mental Health, Veterans Affairs, and the pharmaceutical industry. Author of more than 500 articles and chapters, Dr Stahl is also the author of the bestseller *Stahl's Essential Psychopharmacology* .

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Introduction

This *Guide* is intended to complement *Stahl's Essential Psychopharmacology* . *Stahl's Essential Psychopharmacology* emphasizes mechanisms of action and how psychotropic drugs work upon receptors and enzymes in the brain. This *Guide* gives practical information on how to use these drugs in clinical practice.

It would be impossible to include all available information about any drug in a single work, and no attempt is made here to be comprehensive. The purpose of this *Guide* is instead to integrate the art of clinical practice with the science of psycho-pharmacology. That means including only essential facts in order to keep things short. Unfortunately it also means excluding less critical facts as well as extraneous information, which may nevertheless be useful to the reader but would make the book too long and dilute the most important information. In deciding what to include and what to omit, the author has drawn upon common sense and 30 years of clinical experience with patients. He has also consulted with many experienced clinicians and analyzed the evidence from controlled clinical trials and regulatory filings with government agencies.

In order to meet the needs of the clinician and to facilitate future updates of this *Guide* , the opinions of readers are sincerely solicited. Feedback can be emailed to customerservice@neiglobal.com. Specifically, are the best and most essential psychotropic drugs included here? Do you find any factual errors? Are there agreements or disagreements with any of the opinions expressed here? Are there suggestions for any additional tips or pearls for future editions? Any and all suggestions and comments are welcomed.

All of the selected drugs are presented in the same format in order to facilitate rapid access to information. Specifically, each drug is broken down into five sections, each designated by a unique color background: Therapeutics, Side Effects, Dosing and Use, Special Populations, and The Art of Psychopharmacology, followed by key references.

Therapeutics covers the brand names in major countries; the class of drug; what it is commonly prescribed and approved for by the United States Food and Drug Administration (FDA); how the drug works; how long it takes to work; what to do if it works or if it doesn't work; the best augmenting combinations for partial response or treatment resistance; and the tests (if any) that are required.

Side Effects explains how the drug causes side effects; gives a list of notable, life-threatening, or dangerous side effects; gives a specific rating for weight gain or sedation; and gives advice about how to handle side effects, including best augmenting agents for side effects.

Dosing and Use gives the usual dosing range; dosage forms; how to dose and dosing tips; symptoms of overdose; long-term use; if habit forming, how to stop; pharmacokinetics; drug interactions; when not to use; and other warnings or precautions.

Special Populations gives specific information about any possible renal, hepatic, and cardiac impairments, and any precautions to be taken for treating the elderly, children, adolescents, and pregnant and breast-feeding women.

The Art of Psychopharmacology gives the author's opinions on issues such as the potential advantages and disadvantages of any one drug, the primary target symptoms, and clinical pearls to get the best out of a drug.

In addition, drugs for which switching between medications can be complicated have a special section called The Art of Switching, which includes clinical pearls and graphical representations to help guide the switching process.

There is a list of icons used in this *Guide* following this Introduction and at the back of the *Guide* are several indices. The first is an index by drug name, giving both generic names (uncapitalized) and trade names (capitalized and followed by the generic name in parentheses). The second is an index of common uses for the generic drugs included in the *Guide* and is organized by disorder/symptom. Agents that are approved by the FDA for a particular use are shown in bold. The third index is organized by drug class and lists all the agents that fall within each particular class. In addition to these indices there is a list of abbreviations.

Readers are encouraged to consult standard references[1] and comprehensive psychiatry and pharmacology textbooks for more in-depth information. They are also reminded that the Art of Psychopharmacology section is the author's opinion.

It is strongly advised that readers familiarize themselves with the standard use of these drugs before attempting any of the more exotic uses discussed, such as unusual drug combinations and doses. Reading about both drugs before augmenting one with the other is also strongly recommended. Today's psychopharmacologist should also regularly track blood pressure, weight, and body mass index for most of his or her patients. The dutiful clinician will also check out the drug interactions of non-central nervous system (CNS) drugs with those that act in the CNS, including any prescribed by other clinicians.

Certain drugs may be for experts only, and these might include clozapine, thioridazine, pimozide, nefazodone, and monoamine oxidase (MAO) inhibitors, among others. Off-label uses not approved by the FDA and inadequately studied doses or combinations of drugs may also be for the expert only, who can weigh risks and benefits in the presence of sometimes vague and conflicting evidence. Pregnant or nursing women, or people with two or more psychiatric illnesses, substance abuse, and/or a concomitant medical illness may be suitable patients for the expert only. Controlled substances also require expertise. Use your best judgment as to your level of expertise and realize that we are all learning in this rapidly advancing field. The practice of medicine is often not so much a science as it is an art. It is important to stay within the standards of medical care for the field, and also within your personal comfort zone, while trying to help extremely ill and often difficult patients with medicines that can relieve their suffering and sometimes transform their lives.

Finally, this book is intended to be genuinely helpful for practitioners of psychopharmacology by providing them with the mixture of facts and opinions selected by the author. Ultimately, prescribing choices are the reader's responsibility. Every effort has been made in preparing this book to provide accurate and up-to-date information in accord with accepted standards and practice at the time of publication. Nevertheless, the psychopharmacology field is evolving rapidly and the author and publisher make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. Furthermore, the author and publisher disclaim any responsibility for the continued currency of this information and disclaim all liability for any and all damages, including direct or

consequential damages, resulting from the use of information contained in this book. Doctors recommending and patients using these drugs are strongly advised to pay careful attention to, and consult information provided by, the manufacturer.

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[1] For example, *Physician's Desk Reference* and *Martindale: The Complete Drug Reference* .

List of icons

agomelatine

alcohol dependence treatment

alpha adrenergic blocker

alpha 2 agonist

anticonvulsant

antiparkinson/anticholinergic

benzodiazepine

benzodiazepine receptor antagonist

beta blocker

cholinesterase inhibitor

dopamine 2 antagonist

dopamine 2 partial agonist

dual orexin receptor antagonist

flibanserin

histaminic

lithium

medical food

melanocortin receptor agonist

l-methylfolate

modafinil (wake-promoter)

monoamine oxidase inhibitor

naltrexone/bupropion

nefazodone (serotonin antagonist/reuptake inhibitor)

neuroactive steroid

nicotinic partial agonist

N-methyl-D-aspartate antagonist

noradrenergic and specific serotonergic antidepressant

norepinephrine and dopamine reuptake inhibitor

phentermine/topiramate

phosphodiesterase inhibitor

pimavanserin

sedative-hypnotic

selective norepinephrine reuptake inhibitor

selective serotonin reuptake inhibitor

serotonin-dopamine antagonist

serotonin and norepinephrine reuptake inhibitor

serotonin 1A partial agonist

serotonin partial agonist reuptake inhibitor

sodium oxybate

stimulant

thyroid hormone

trazodone (serotonin antagonist/reuptake inhibitor)

tricyclic/tetracyclic antidepressant

vesicular monoamine transporter 2 inhibitor

vortioxetine

How the drug works, mechanism of action

Best augmenting agents to add for partial response or treatment resistance

Life-threatening or dangerous side effects

Weight Gain : Degrees of weight gain associated with the drug, with unusual signifying that weight gain has been reported but is not expected; not unusual signifying that weight gain occurs in a significant minority; common signifying that many experience weight gain and/or it can be significant in amount; and problematic signifying that weight gain occurs frequently, can be significant in amount, and may be a health problem in some patients

Sedation : Degrees of sedation associated with the drug, with unusual signifying that sedation has been reported but is not expected; not unusual signifying that sedation occurs in a significant minority; common signifying that many experience sedation and/or it can be significant in amount; and problematic signifying that sedation occurs frequently, can be significant in amount, and may be a health problem in some patients

Tips for dosing based on the clinical expertise of the author

Drug interactions that may occur

Warnings and precautions regarding use of the drug

Dosing and other information specific to children and adolescents

Information regarding use of the drug during pregnancy

Clinical pearls of information based on the clinical expertise of the author

The art of switching

Suggested reading

Acamprosate

Therapeutics

Brands

- Campral
- *see index for additional brand names*

Generic?

Not in USA

Class

- Neuroscience-based Nomenclature: glutamate multimodal (Glu-MM)
- Alcohol dependence treatment

Commonly Prescribed for

(bold for FDA approved)

- **Maintenance of alcohol abstinence**

How the Drug Works

- Theoretically reduces excitatory glutamate neurotransmission and increases inhibitory gamma-aminobutyric acid (GABA) neurotransmission

- Binds to and blocks certain glutamate receptors, including metabotropic glutamate receptors
- Because withdrawal of alcohol following chronic administration can lead to excessive glutamate activity and deficient GABA activity, acamprosate can act as “artificial alcohol” to mitigate these effects

How Long Until It Works

- Has demonstrated efficacy in trials lasting between 13 and 52 weeks

If It Works

- Increases abstinence from alcohol

If It Doesn’t Work

- Evaluate for and address contributing factors
- Consider switching to another agent
- Consider augmenting with naltrexone

 Best Augmenting Combos for Partial Response or Treatment Resistance

- Naltrexone
- Augmentation therapy may be more effective than monotherapy
- Augmentation with behavioral, educational, and/or supportive therapy in groups or as an individual is probably key to successful treatment

Tests

- None for healthy individuals

Side Effects

How Drug Causes Side Effects

- Theoretically, behavioral side effects due to changes in neurotransmitter concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions
- Gastrointestinal side effects may be related to large doses of a drug that is an amino acid derivative, increasing osmotic absorption in the gastrointestinal tract

Notable Side Effects

- Diarrhea, nausea
- Anxiety, depression

Life-Threatening or Dangerous Side Effects

- Suicidal ideation and behavior (suicidality)

Weight Gain

- Reported but not expected

Sedation

- Reported but not expected

What to Do About Side Effects

- Wait
- Adjust dose
- If side effects persist, discontinue use

Best Augmenting Agents for Side Effects

- Dose reduction or switching to another agent may be more effective since most side effects cannot be improved with an augmenting agent

Dosing and Use

Usual Dosage Range

- 666 mg three times daily (>60 kg)
- 666 mg two times daily (<60 kg)

Dosage Forms

- Tablet 333 mg

How to Dose

- Patient should begin treatment as soon as possible after achieving abstinence
- Recommended dose is 666 mg three times daily; titration is not required

Dosing Tips

- Providing educational materials and counseling in combination with acamprosate treatment can increase the chances of success
- Patients should be advised to continue treatment even if relapse occurs, and to disclose any renewed drinking
- Although absorption of acamprosate is not affected by food, it may aid adherence if patients who regularly eat three meals per day take each dose with a meal
- Adherence with three times daily dosing can be a problem; having patient focus on frequent oral dosing of drug rather than frequent drinking may be helpful in some patients

Overdose

- Limited available data; diarrhea

Long-Term Use

- Has been studied in trials up to 1 year

Habit Forming

- No

How to Stop

- Taper not necessary

Pharmacokinetics

- Terminal half-life 20–33 hours
- Excreted unchanged via the kidneys

 Drug Interactions

- Does not inhibit hepatic enzymes, and thus is unlikely to affect plasma concentrations of drugs metabolized by those enzymes
- Is not hepatically metabolized and thus is unlikely to be affected by drugs that induce or inhibit hepatic enzymes
- Concomitant administration with naltrexone may increase plasma levels of acamprosate, but this does not appear to be clinically significant and dose adjustment is not recommended

⚠ Other Warnings/Precautions

- Monitor patients for emergence of depressed mood or suicidal ideation and behavior (suicidality)
- Use cautiously in individuals with known psychiatric illness

Do Not Use

- If patient has severe renal impairment
- If there is a proven allergy to acamprosate

Special Populations

Renal Impairment

- For moderate impairment, recommended dose is 333 mg three times daily
- Contraindicated in severe impairment

Hepatic Impairment

- Dose adjustment not generally necessary

Cardiac Impairment

- Limited data available

Elderly

- Some patients may tolerate lower doses better
- Consider monitoring renal function

 Children and Adolescents

- Safety and efficacy have not been established

Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- In animal studies, acamprosate demonstrated teratogenicity in doses approximately equal to the human dose (rat studies) and in doses approximately 3 times the human dose (rabbit studies)
- Pregnant women needing to stop drinking may consider behavioral therapy before pharmacotherapy
- Not generally recommended for use during pregnancy, especially during first trimester

Breast Feeding

- Unknown if acamprosate is secreted in human breast milk, but all psychotropics are assumed to be secreted in breast milk
- Recommended either to discontinue drug or bottle feed

The Art of Psychopharmacology

Potential Advantages

- Individuals who have recently abstained from alcohol
- For the chronic daily drinker

Potential Disadvantages

- Individuals who are not abstinent at time of treatment initiation
- For binge drinkers

Primary Target Symptoms

- Alcohol dependence

Pearls

- Because acamprosate serves as "artificial alcohol," it may be less effective in situations in which the individual has not yet abstained from alcohol or suffers a relapse
- Thus acamprosate may be a preferred treatment if the goal is complete abstinence, but may not be preferred if the goal is reduced-risk drinking

Suggested Reading

Anton RF , O'Malley SS , Ciraulo DA , et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial . *JAMA* 2006 ;**295** (17): 2003 –17.

Kranzler HR , Gage A . Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials . *Am J Addictions* 2008 ; **17** :70 –6.

Rosner S , Leucht P , Soyka M . Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a met-analysis with unreported outcomes . *J Psychopharmacol* 2008 ;**22** :11 –23 .