

Overview of Trends in Modern Psychopharmacology

By Stephen M. Stahl, MD, PhD

INTRODUCTION

Beginning this month, *CNS Spectrums* will publish this column, "Trends in Psychopharmacology," on a bi-monthly basis. Developments in psychopharmacology are proceeding at a fast pace, and this column will cover important and emerging areas from the field in a format that will be brief, and hopefully understandable. Topics will include what is new, "hot," controversial, or informative in the field, and, of course, suggestions for future columns are always welcome.

DRUGS IN LATE STAGE DEVELOPMENT

New psychopharmacologic treatments of interest include several late-stage products, most of which have mechanisms similar to products already on the market.¹ Thus, in the area of depression, there are drugs that are active metabolites of known antidepressants (desvenlafaxine and radafaxine), and drugs that combine actions of known agents (ie, the "triple" reuptake inhibitors that block the transporters for serotonin, norepinephrine, and dopamine) (Table 1). As this is a novel combination of mechanisms and there are few agents available for depression that act on dopamine, triple reuptake inhibitors may provide a therapeutic advance, especially for patients with symptoms hypothetically linked to dopamine, such as cognitive problems, sexual dysfunction, lack of motivation, and fatigue. Other agents in late-stage development for depression include a controlled-release formulation of the serotonin (5-HT)_{1A} partial agonist, gepirone, and

an interesting dual-action agent, agomelatine, which combines agonist actions at melatonin 1 and 2 receptors with antagonist actions at 5-HT_{2C} receptors (Table 1).

In the area of schizophrenia, late-stage products include new atypical antipsychotics, such as asenapine and iloperidone, as well as a novel dopamine partial agonist, bifeprunox (Table 2). These same agents are under development for bipolar disorder, especially for bipolar depression. An active metabolite of a known anticonvulsant, licarbazepine, is also being tested in bipolar disorder (Table 3).

Novel hypnotics in late-stage testing include modulators of γ -aminobutyric acid A receptors

TABLE 1.
Key Antidepressants in Development

- Desvenlafaxine (metabolite of venlafaxine)
- Radafaxine (metabolite of bupropion)
- Triple reuptake inhibitors
- Gepirone ER
- Agomelatine
- β_3 agonists
- NK₂ antagonists
- CRF₁ antagonists
- Vasopressin 1B antagonists
- Nemifitide

ER=extended release; NK=neurokinin; CRF=corticotropin releasing factor.
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(indiplon and gaboxadol), selective histamine 1 antagonists (very low dose doxepin, very low doses of the active enantiomer of mirtazapine), and several selective antagonists/inverse agonists of 5-HT_{2A} receptors (Table 3).

In the area of attention-deficit/hyperactivity disorder, new agents in late-stage development include a lysine-prodrug of amphetamine that may reduce abuse potential, a longer controlled-release version of mixed amphetamine salts, and a sustained release formulation of the α -2-adrenergic agent guanfacine (Table 3)

As these agents in late stage testing progress from development to FDA approval, they have the potential to impact clinical practice greatly. We will cover specific agents in more detail as the data emerge.

NOVEL AGENTS EARLIER IN DEVELOPMENT

A number of novel agents are also proceeding into clinical development. Since they act by novel mechanisms, it will be useful to explore the rationale behind such agents in future articles. For depression, this includes the novel β ₃ agonists, neurokinin 2 antagonists, corticotropin releasing factor antagonists, vasopressin 1_B antagonists, an injectable pentapeptide, nemifitide, and many

more (Table 1). For schizophrenia, this includes agents working by non-dopaminergic mechanisms, such as 5-HT_{2C} agonists; glycine transport inhibitors that boost co-agonist glycine actions at *N*-methyl-D-aspartate glutamate receptors; positive allosteric modulators of *N*-methyl-D-aspartate as well as post-synaptic metabotropic glutamate receptors; and antagonists of presynaptic metabotropic glutamate autoreceptors (Table 2). In schizophrenia, there are a number of augmentation strategies for novel mechanisms to be added to atypical antipsychotics, including 5-HT_{2A} inverse agonists and 5-HT_{1A} antagonists (Table 2). For treatment of insomnia, there are novel histamine 1 inverse agonists, and for smoking cessation, α ₄ β ₂ selective nicotinic acetylcholine receptor partial agonists (eg, varenicline) (Table 3).

The list is growing and encouraging for future therapeutic development in psychopharmacology. As these agents progress in clinical development, their mechanisms of action will be a major focus of this column.

EXPANDING THE BOUNDARIES OF PSYCHOPHARMACOLOGY PRACTICE

The field of psychopharmacology is dynamic and ever changing. Now, psychopharmacologists are treating disorders that have been recently better clarified, such as bipolar depression and chronic insomnia (Table 4). Areas related to psy-

TABLE 2.
Key Antipsychotics in Development

Paliperidone (metabolite of risperidone): just approved
Asenapine
Iloperidone
Bifeprunox (dopamine partial agonist)
5-HT _{2C} agonists
Glycine transport inhibitors
Glycine agonists
Positive allosteric modulators of NMDA glutamate receptors
Positive allosteric modulators of postsynaptic metabotropic glutamate receptors
Antagonists of presynaptic metabotropic glutamate autoreceptors
5-HT _{2A} inverse antagonists (for augmentation)
5-HT _{1A} antagonists (for augmentation)

5-HT=serotonin; NMDA=*N*-methyl-D-aspartate.
Stahl SM. *CNS Spectr*. Vol 12, No 2. 2007.

TABLE 3.
Other Key Agents in Development

Licarbazepine (bipolar disorder)
Indiplon (insomnia)
Gaboxadol (insomnia)
Histamine 1 selective antagonists (very low dose doxepin, mirtazapine active isomer (insomnia))
Histamine 1 inverse agonists (insomnia)
5-HT _{2A} antagonists/inverse agonists (insomnia)
lys-dex-amphetamine (lysine linked to dexamphetamine) (ADHD)
Longer extended release of mixed amphetamine salts (ADHD)
Guanfacine oral sustained-release (ADHD)
Varenicline (α ₄ β ₂ selective nicotinic acetylcholine partial agonist) (smoking cessation): recently approved

5-HT=serotonin; ADHD=attention-deficit/hyperactivity disorder.
Stahl SM. *CNS Spectr*. Vol 12, No 2. 2007.

chopharmacology that now require an expertise include monitoring insulin resistance and dyslipidemia (eg, with fasting triglycerides) as well as weight and glucose in patients receiving atypical antipsychotics (Table 4).

Obesity is also poised for psychopharmacologic treatment approaches (eg, with hormone derivatives of amylin, leptin, and ghrelin and with agents, such as bupropion, topiramate, and zonisamide, perhaps in combinations). Substance abuse now has numerous emerging treatments, but these are not yet used in great numbers by psychopharmacologists, including the new injectable naltrexone and acamprosate for alcohol abuse, buprenorphine for opiate abuse, and varenicline for smoking cessation. Psychopharmacologists will increasingly be able to treat numerous other disorders not traditionally part of practice, including hypoactive sexual desire disorder, fibromyalgia, perimenopausal vasomotor symptoms, geriatric depression, numerous dementias, and even gambling (Table 4). Psychopharmacologists may also need to become increasingly sophisticated with devices as well as drugs in the future, including not only classical electroconvulsive therapy but also vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation (Table 4).

TABLE 4.
Expanding the Boundaries of Psychopharmacology Practice

Bipolar depression
Chronic insomnia
Monitoring insulin resistance and dyslipidemia
Obesity
Substance abuse (alcohol, opiates, smoking cessation, stimulants, other)
Hypoactive sexual desire disorder
Fibromyalgia
Vasomotor symptoms of perimenopause
Geriatric depression
Dementias
Electroconvulsive therapy
Vagus nerve stimulation
Transcranial magnetic stimulation
Deep brain stimulation

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CONCLUSION

These paradigm shifts entering the field of psychopharmacology will be discussed in future columns. The outlook for this field seems to be exciting, with many new developments and changes afoot. We will strive to be a source of readable and informative updates in psychopharmacology for readers of *CNS Spectrums*. **CNS**

REFERENCE

1. Stahl SM. Finding what you are not looking for: strategies for developing novel treatments in psychiatry. *NeuroRx*. 2006;3:3-9.

Dr. Stahl's next column will appear in the April issue of CNS Spectrums.

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