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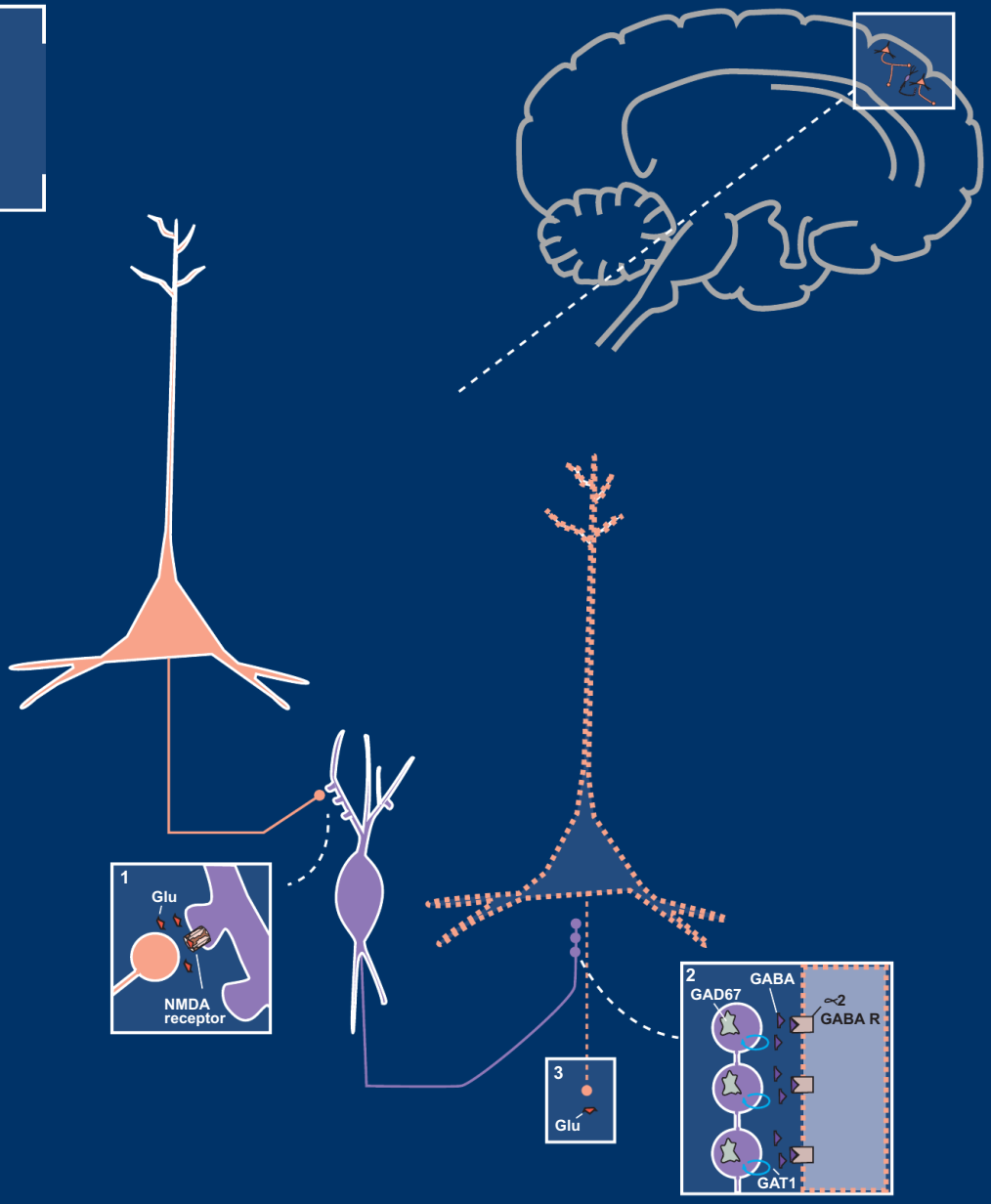

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CNS SPECTRUMS

EDITOR-IN-CHIEF: **STEPHEN M. STAHL**

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CNS SPECTRUMS

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Aims and Scope

CNS Spectrums aims to be the premiere journal covering all aspects of clinical neurosciences, neurotherapeutics and neurospsychopharmacology. From 2012 the journal will primarily focus on the publication of authoritative, cross-disciplinary

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Cover Image: The image on the cover shows a hypothetical model whereby glutamate is released from an intracortical pyramidal neuron and binds to an NMDA receptor on a GABA-ergic interneuron. GABA is then released and binds to receptors on the axon of another glutamate pyramidal neuron. This inhibits the neuron, thus reducing the release of cortical glutamate. The GABA interneuron and its NMDA synapse from the first neuron to the second is the hypothetical site of glutamate dysfunction in schizophrenia.

Stahl's Essential Psychopharmacology, 4th edition, by Stephen M. Stahl

review and opinion material publishing advances and controversial issues with pertinence to the clinician. In particular we aim to publish reviews and articles in translational neuroscience, biological psychiatry and neuropsychopharmacology that explain clinically relevant neuroscience discoveries in a way that makes these findings accessible and understandable to clinicians and clinical investigators. We will emphasize new therapeutics of all types in clinical neurosciences, mental health, psychiatry, and neurology, especially first in man studies and proof of concept studies. Our focus will be not just drugs, but novel psychotherapies and neurostimulation therapeutics as well. *CNS Spectrums* will in addition, continue to publish original research and commentaries that focus on emergent areas of research. Subject coverage shall span the full spectrum of neuropsychiatry focusing on translational issues and those crossing traditional boundaries between neurology and psychiatry.

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BRAINSTORMS—Clinical Neuroscience Update

Classifying psychotropic drugs by mode of action and not by target disorder

Stephen M. Stahl

ISSUE:

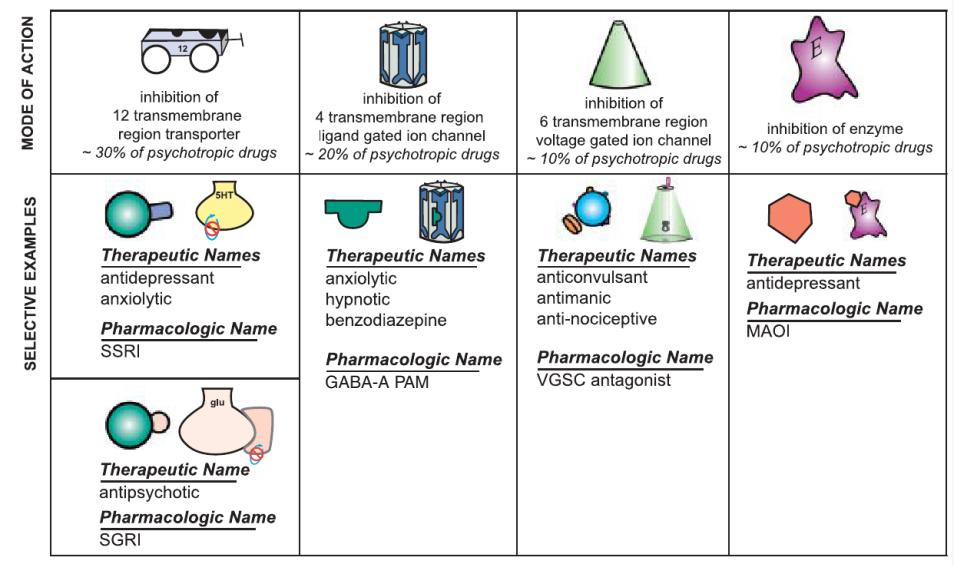
Psychotropic drugs are traditionally classified by the first disorder they are proven to target (eg, as antidepressants or antipsychotics). However, these names are becoming increasingly confusing, as many drugs have multiple therapeutic actions. A more rational nomenclature categorizes psychotropic drugs by their pharmacologic mode of action.

Take-Home Points

1. Agents called "antidepressants" also treat multiple anxiety disorders such as generalized anxiety disorder, posttraumatic stress disorder, panic disorder, and social anxiety disorder; impulsive/compulsive spectrum disorders, such as obsessive compulsive disorder; eating disorders, such as bulimia; and pain conditions, such as neuropathic pain. Agents called "antipsychotics" are also proven to have efficacy in unipolar treatment-resistant depression, in acute bipolar mania, and in bipolar depression.
2. Rather than classifying psychotropic drugs by therapeutic target(s), a paradigm shift is afoot to classify drugs by their known and most potent pharmacologic mode(s) of actions.
3. There are 5 known modes of action of psychotropic drugs:
   a. Inhibition of a neurotransmitter transporter
   b. Agonist, partial agonist, or antagonist actions at a G-protein linked receptor
   c. Antagonist actions at a ligand-gated ion channel
   d. Antagonist actions at a voltage-gated ion channel
   e. Inhibition of an enzyme
4. Psychotropic drugs can be selective or can have more than one pharmacologic action:
   a. Single action agents with a single mode of action are *selective*.
   b. Agents with multiple actions at the same mode (eg, simultaneous actions at multiple G-protein linked receptors) are *multifunctional*.
   c. Agents with actions at more than one mode are *multimodal*.

Sixty years ago, when psychotropic drugs were introduced, their pharmacologic mechanisms of action were unknown, and they were simply "antipsychotics" or "antidepressants" or "tranquilizers." Today, we have a much better understanding of the pharmacologic actions of psychotropic drugs, which are now categorized according to 5 modes of action[1] (these are listed above in the Take-Home Points). Some drugs have a single known mode of action (Table 1), but most have multiple pharmacologic actions (Tables 2 and 3). Originally, drugs with more than one pharmacologic action were thought to be "dirty," with only one mechanism thought to be responsible for therapeutic effects, and the others for side effects. Now, it is increasingly clear that drugs can be selective, but they can also have multiple concomitant therapeutic actions—a sort of "intramolecular polypharmacy" that may create therapeutic synergies where total therapeutic actions are greater than the sum of the pharmacologic parts. Those agents with more than one therapeutic action can have 2 or more actions at a single mode, and are called multifunctional (Table 2). Other agents can

Table 1. *Examples of selective modes of action for various psychotropic drugs acting at 4 of the 5 known modes of action*



Two examples of selective inhibition of a neurotransmitter transporter are shown in column 1: the first is for agents targeting the serotonin (5HT) transporter also known as SERT, and these agents are already named for their selective action, called selective serotonin reuptake inhibitors (SSRIs). The second example is a new drug class in clinical development that targets the transporter for the amino acid neurotransmitter glycine, namely the glycine transporter type 1 (GlyT1) transporter on glial cells and glutamate neurons; these agents are called selective glycine reuptake inhibitors (SGRIs). A ligand gated ion channel is selectively targeted in the second column. In this example, a benzodiazepine targets the GABA-A receptor and is a positive allosteric modulator (PAM), which is why the pharmacologic class is GABA-A PAM. In the third column, an agent selectively targets voltage gated sodium channels (VGSCs) and is called a VGSC antagonist. In the fourth column, a drug selectively targets an enzyme, monoamine oxidase (MAO), and is known as an MAOI or MAO inhibitor.

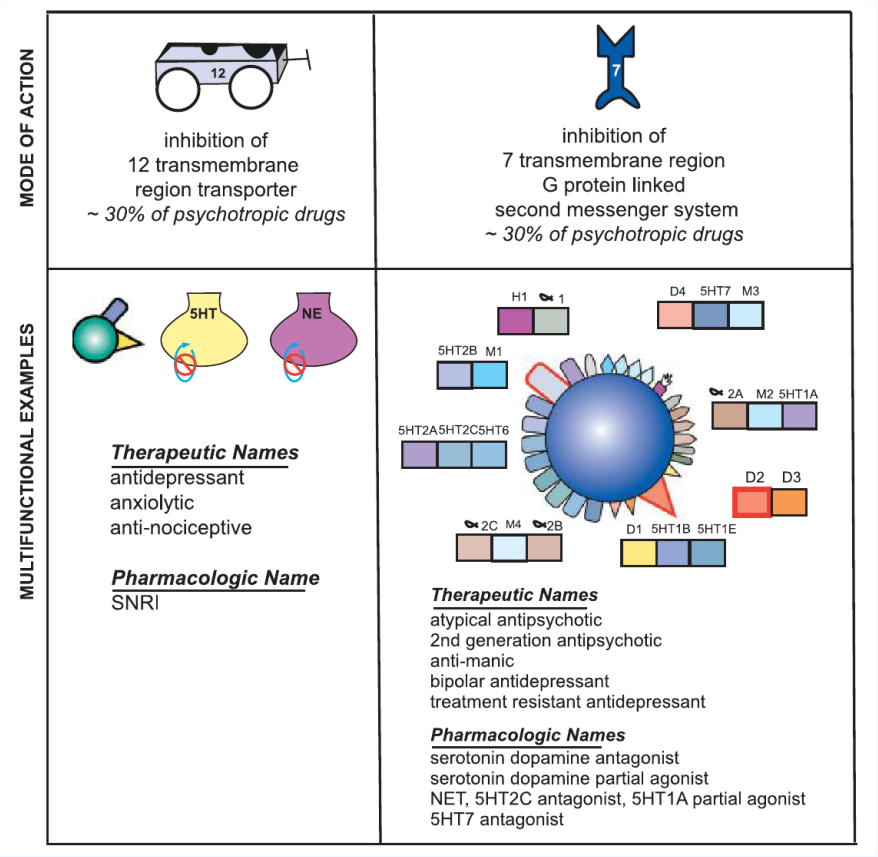
have actions at more than one mode, and are called multimodal (Table 3).

An international consensus committee with representatives from the American College of Neuropsychopharmacology (ACNP), the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), and the Asian College of Neuropsychopharmacology (AsCNP) has developed a position statement that psychotropic drugs should be named for their principle pharmacologic action(s).[2] Specifically, this group proposes a multiaxial system for nomenclature in neuropsychopharmacology to clarify and expand the known pharmacology, neurobiological activity, and clinical actions of each psychotropic drug (Table 4).[2] These concepts are applied to the primary drug classes here in Tables 1–3.

References

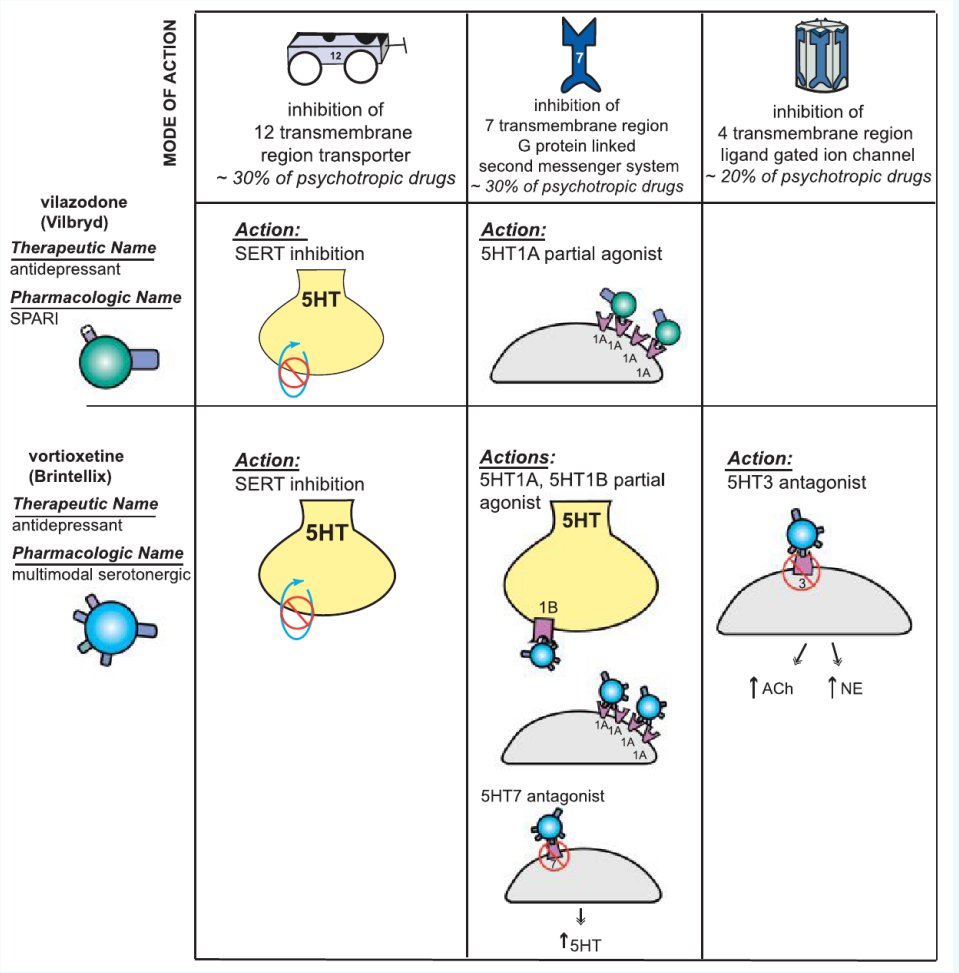
1. Stahl SM. *Stahl's Essential Psychopharmacology*, 4th ed. New York: Cambridge University Press; 2013.
2. Zohar J, Nutt DJ, Kupfer DJ, *et al*. A proposal for an update in nomenclature of neuropsychopharmacology. *Eur Neuropsychopharmacol*. In press.

Table 2. *Examples of multifunctional drugs*



When a psychotropic drug acts at two or more targets within a single mode of action, it is called multifunctional. On the left, an agent targets two monoamine transporters, namely the serotonin (5HT) transporter (SERT) and the norepinephrine (NE) transporter (NET). These agents are already commonly known as serotonin norepinephrine reuptake inhibitors (SNRIs). The second column shows the drug class that has the most known simultaneous mechanisms of action, all of which target G protein linked receptors. This drug class, commonly called atypical antipsychotics or second generation antipsychotics, is the source of much confusion because these agents are expanding their use to many other therapeutic areas. These agents all are either serotonin dopamine antagonists (SDAs) or serotonin dopamine partial agonists (SDPAs), which is why they are thought to have antipsychotic actions. Antidepressant actions, on the other hand, are linked to different pharmacologic mechanisms, and some agents such as quetiapine and norquetiapine are also norepinephrine transporter (NET) and 5HT2C antagonists plus 5HT1A partial agonists; other agents in this class such as lurasidone are also potent 5HT7 antagonists. Such additional pharmacologic properties create a second class for these complex agents and this second class may explain antidepressant actions.

Table 3. *Examples of multimodal drugs*



When a psychotropic drugs acts at two more modes, it is called multimodal. Two examples are shown here, the first for an agent that targets both a G-protein linked receptor and a monoamine transporter. Specifically, the agent vilazodone is a partial agonist at 5HT1A receptors and also blocks the serotonin transporter SERT. Thus, its pharmacologic name is a serotonin partial agonist and reuptake inhibitor (SPARI). The second example is an agent that has 5 known mechanisms of action, including targeting 3 different modes, namely a monoamine transporter, 3 different G-protein linked receptors, and a ligand-gated ion channel. Specifically, the late stage compound vortioxetine is a serotonin transporter (SERT) inhibitor, as well as a partial agonist at both 5HT1A and 5HT1B receptors, and an antagonist at 5HT7 receptors, all three of these belonging to the G-protein linked receptor mode of action. Finally, vortioxetine also is an antagonist at 5HT3 receptors, which are ligand gated ion channels.

Table 4. *Proposed template for a multi-axial psychopharmacological nomenclature*

Axis 1	**Class**		
	Subtype		
Axis 2	**Name (primary pharmacological targets)**		
Axis 3	Neurobiological activity		
		Animal	Human
	Neurotransmitter effects		
	Phenotypes		
	Brain circuits		
	Gene expression		
	Physiological		
Axis 4	**Clinical observations (including major side effects)**		
Axis 5	**Indications**		

Axis 1 for psychotropic drug nomenclature lists the broad pharmacological class and subtype of the drug, whereas **Axis 2** is for the actual name of the drug, representing the specific main pharmacological target(s) of that drug. **Axis 3** concerns the known neurobiological activity of the drug, often a consequence of its Axis 1 and Axis 2 actions, and including its neurotransmitter effects, phenotypes, brain circuits, gene expression, and physiological effects in both animals and humans. **Axis 4** details the clinical observations, which include major known side effects of the drug. **Axis 5** gives the clinical indications currently approved for the drug (see Zohar *et al*[2]).

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REVIEW ARTICLE

Pharmacokinetics and pharmacodinamics of psychotropic drugs: effect of sex

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Data on the specific effects of sex on pharmacokinetics, as well as tolerability, safety, and efficacy of psychotropic medications are still meager, mainly because only recently sex-related issues have attracted a certain degree of interest within the pharmacological domain. Therefore, with the present study, we aimed to provide a comprehensive review of the literature on this topic, through careful MEDLINE and PubMed searches of the years 1990–2012.

Generally, data on pharmacokinetics are more consistent and numerous than those on pharmacodynamics. Sex-related differences have been reported for several parameters that influence pharmacokinetics, such as gastric acidity, intestinal motility, body weight and composition, blood volume, liver enzymes (mainly the cytochrome P450), or renal excretion, which may alter plasma drug levels. Sex-related peculiarities may also account for a different sensitivity of men and women to side effects and toxicity of psychotropic drugs. Further, some differences in drug response, mainly to antipsychotics and antidepressants, have been described.

Further studies are, however, necessary to explore more thoroughly the impact of sex on the pharmacokinetics and pharmacodynamics of psychotropic drugs, in order to reach the most appropriate and tailored prescription for each patient.

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Key words: Antipsychotics, benzodiazepines, gender, psychotropic drugs, SSRIs, tricyclics.

FOCUS POINTS

- The pharmacokinetic profile of a given drug is different in the two sexes at the levels of absorption, distribution, metabolism, and elimination.
- The different pharmacokinetic characteristics in men and women may influence plasma levels of psychotropic drugs and, perhaps, their effectiveness.
- Sex-related peculiarities may also account for a different sensitivity of men and women to the side-effects of psychotropic drugs.
- Men and women seem to respond differently to some antipsychotics and antidepressants.

Introduction

In spite of the empirical evidence showing that, generally, psychotropic drugs are more commonly used (and abused) by women, who are thus more exposed to adverse events,[1] data regarding the specific effects of sex on drug tolerability, safety, and efficacy are still poor. Converging, albeit scattered, findings would suggest that sex plays an important role in determining the pharmacokinetic profile of psychotropic drugs, while data on pharmacodynamics are few in number. It is, however, interesting to underline that prior to 1993, women were rarely included in bioequivalence trials, as it was believed that the inclusion of women would have caused a significantly higher interindividual variability, resulting in the need for larger sample sizes.

The aim of this work is to review the available literature regarding the possible impacts of gender differences on the pharmacokinetics and the pharmacodynamics of psychotropic drugs. For this purpose, we carried out MEDLINE and PubMed searches of the years 1990–2012 with the following keywords: psychotropic drugs, sex, benzodiazepines (BDZs), typical and atypical antipsychotics, antidepressants, tricyclics (TCAs), and selective serotonin reuptake inhibitors (SSRIs).

Absorption

The absorption of a given drug depends on multiple factors—some related to the characteristics of the drug, such as physiochemical properties, formulation, and route of administration, and some to the gastrointestinal (GI) environment, if given orally. Absorption is affected by differences in luminal pH along the GI tract, surface area per luminal volume, blood perfusion,

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Table 1. *Effect of different parameters on drug absorption in women (W) and men (M)*

	W M	Effects on drug plasma levels
Gastric elimination	Reduced/increased	Reduced/increased
Gastric acidity	Reduced/increased	Increased/reduced
Activity of gastric enzymes	Reduced/increased	Increased/Reduced
Intestinal transit time	Faster/slower	Reduced/increased

presence of bile and mucus, and nature of epithelial membranes.

Women, as compared with men, show a reduced capacity of gastric elimination[2,3] and a shorter time of intestinal transit,[4] which may lead to decreased drug plasma levels (Table 1). Women show also lower levels of gastric acidity compared to men,[3,5] and, therefore, compounds that tend to have a basic pH, such as BDZs or TCAs, are absorbed more rapidly and reach higher concentrations.[3,6] In addition, some gastric enzymes are less active in women, and this characteristic also would contribute to increased plasma concentrations.

Sex differences have been also reported for bile acid composition, which is another factor that may influence the solubility of different drugs. Men tend to present higher concentrations of cholic acid, while women present higher concentrations of chenodeoxycholic acid.[7]

A review of 26 studies submitted over a 20-year period to the Food and Drug Administration (FDA), the major U.S. drug regulation agency, revealed some sex differences in bioequivalence, with women showing significantly greater drug absorption (Cmax) and area under the concentration time curve than men. However, these findings should be interpreted with caution, as the sample size of these studies was quite small (no more than 10 men and 10 women), and the statistical significance of the difference decreased after correcting for weight.[8]

Distribution

The volume of distribution of a drug is determined by different factors, including body weight, percentage of fatty mass, the degree of local blood flow, and binding to proteins. Women are characterized by lower body weight, but drug dosing in adults is not currently adjusted for body weight. Further, women show reduced blood volume and a larger amount of body fat mass than men.[9] The first two characteristics would provoke higher drug concentrations in women, while the greater percentage of fat mass would cause a larger distribution volume and thus, at least initially, lower plasma concentrations of a lipid-soluble compound[3] (Table 2). Several psychotropic drugs, such as BDZs, are characterized by a high lipophilicity; they tend to accumulate easily in the adipose tissue, and this may lead to a significant increase in their half-life.[10] Given that the fat mass increases with age, these drugs tend to accumulate more in elderly women who are at greater risk for this effect.[11,12] Nevertheless, despite the fact that elderly women are among those who most often take psychotropic drugs, results of systematic and reliable studies to assess the potential role of sex and age interaction on drug plasma levels are not yet available.[13,14]

Table 2. *Effect of different parameters on drug distribution in women (W) and men (M)*

	W M	Effects on drug plasma levels
Body weight	Less/more	Increased/reduced
Volume of distribution	Less/more	Increased/reduced
Lipid mass	More/less	Reduced*/increased

*Vouly initially, as over time, accumulation may occur imeressing half-life of a drug.

Once in the blood stream, drugs bind to plasma proteins, mainly to albumin and to alpha-1 glycoprotein acid. The total concentration of the drugs depends, thus, on the amount bound to proteins compared to the free quantity (unbound), but generally only the free quantity is active, and can pass through the blood–brain barrier and reach the central nervous system (CNS). While albumin does not seem to be influenced by gonadal steroids,[15] acid glycoprotein (AAG) may be lower in women[16–18] and is decreased by estradiol,[16,19] an effect that should increase the proportion of free drug; however, some disagreement exists.[15,17] Drugs bound by alpha-1 glycoprotein acid include triazolam, amitriptyline, desipramine, imipramine, doxepine, nortriptyline, reboxetine, chlorpromazine, thioridazine, and olanzapine.[20]

Generally speaking, the binding capacity of the plasma proteins seems to be lower in women than in men. This difference has a certain importance for several psychotropic compounds that generally show a high protein binding. Benzodiazepines circulate bound to plasma proteins in a percentage of 99%. Some serotonin reuptake inhibitor (SSRI) antidepressants, such

Table 3. *Antidepressants and BDZ binding to plasma proteins*

Binding to proteins	%
BDZ	99
Fluoxetine, sertraline, paroxetine	>95
Nefazodone	>95
TCA	75–95
Fluvoxamine	77
Citalopram	50
Venlafaxine	38

as fluoxetine and paroxetine, are bound in percentages higher than 95%.[21] By contrast, TCAs and fluvoxamine are only moderately bound (75% and 77%, respectively),[22,23] and citalopram and venlafaxine are bound even less (50% and 38%, respectively)[24] (Table 3).

Simultaneous administration of two drugs with elevated protein binding may cause one of the two to be displaced, thus increasing its free amount, which may become toxic and cause severe side effects. As already mentioned, BDZs and TCAs are bound to plasmatic proteins in a moderate to strong way,[25,26] and, therefore, even a relative increase in the concentrations of TCAs may be clinically relevant in women, where these drugs have a relatively low therapeutic index. Therefore, the differences in protein binding may contribute to a greater risk for side effects and toxicity of TCAs in women than in men. Most SSRIs, with the exception of fluvoxamine and citalopram, are characterized by a high percentage of protein binding, although the type of binding is weak and involves mainly alpha1-glycoprotein acid.[26] Therefore the simultaneous administration of high protein-binding drugs, such as the anticonvulsants or warfarin, may lead to a dissociation of the SSRIs from the protein binding. Nevertheless, SSRIs have a wide safety interval, and even high plasma levels may not be toxic.

Elimination

Two processes, metabolism and elimination, are responsible separately or together for drug inactivation. Drugs are eliminated from the body mainly by hepatic, renal, or pulmonary routes and also, to a lower extent, by sweat, tears, and breast milk.

Hepatic clearance of drugs is a function of liver blood flow and hepatic enzyme activity. Hepatic blood flow is lower in women than in men, but also sex differences in hepatic enzymes are important. It has been reported that the expression of P-glycoprotein, which regulates the biliary excretion of certain drugs, is 2-fold lower in women than in men, maybe due to hormonal effects.[7]

Metabolism

The metabolism of most psychotropic drugs occurs in the liver due to the action of different enzymatic systems. Both hydroxylation and glucuronidation are slower in women than in men, with consequent higher drug plasma concentrations in women.[26,27] Moreover, in comparison with men, women show lower renal clearance rates, which are probably associated with a reduced capacity for glomerular filtration.[3] Since many psychotropic substances are excreted through the kidneys, both the metabolic processes and the filtration of psychotropic drugs are slower in women, and this provokes a generally slower elimination of the different compounds.

The enzymatic system of the cytochrome P450 (CYP)

A substantial amount of the hepatic metabolism of psychotropic drugs is regulated by the action of the enzymatic system of the cytochrome P450 (CYP), which is composed of more than 30 types of different isozymes.[21,26] These are a large family of related enzymes located in the smooth endoplasmic reticulum of the cell. While the CYP enzymes are all coded for by autosomal chromosomes, it is possible that sex-related differences in pharmacokinetics arise from variations in the regulation of the expression and activity of CYP enzymes through endogenous hormonal influences.[7,28,29]

The isozymes CYP2D6, CYP3A4, CYP1A1/2, and CYP2C19 are responsible for the metabolic processes of most psychotropic drugs, and also of many other commonly prescribed drugs, such as beta-blockers, opiate analgesics, anticonvulsants, corticosteroid compounds, and some antibiotics.

CYP2D6

The isozyme CYP2D6 is responsible for the metabolism of most antidepressants, haloperidol, and pain killers. Its inhibition, therefore, provokes increased plasma concentrations of a given compound, and this may lead to a toxic reaction when a SSRI is co-administered with a TCA or an anti-arrhythmic compound.[21] Although the enzyme CYP2D6 has become remarkably famous for its role in the interaction between one drug and another, no sex differences have been described in its activity.[6,30]

Because CYP2D6 activity is increased during pregnancy,[31] it would be expected that female sex steroids influence CYP2D6 activity. However, some findings do not support this notion.[32–34]

CYP2C19

Sex differences have been reported for the isozyme CYP2C19. Women, in fact, seem to show a greater

enzymatic activity compared to men.[6,30] This is relevant for several antidepressants (clomipramine, imipramine, and citalopram) and BDZs (diazepam) that are metabolized by this system, so that women have a faster metabolism and a lower plasma concentration of the same drugs.[27,35,36] There is some evidence of sex-related differences in the activity of CYP2C19 that are ethnically dependent, although a recent study suggested that the population data may be confounded by oral contraceptive use. While using S-mephenytoin as a probe, CYP2C19 activity was higher in Chinese women than men. By contrast, a lower activity was demonstrated in African Americans[37] and Jewish Israeli[38] women than in men. There was no sex difference in activity in Saudi Arabians and Filipinos.[39] In one large population study of Dutch Caucasians, CYP2C19 activity was 40% greater in men than women.[40] In a population study in Sweden using S-mephenytoin as a probe, CYP2C19 activity was found to be 61% lower in women receiving oral contraceptives compared with women not taking these drugs.[41] However, aside from this last study, all the population studies just mentioned failed to report oral contraceptive use, so that it is not clear if CYP2C19 activity is sex- or ethnicity-dependent, or if the differences are due only to oral contraceptive use.

CYP2C9

CYP2C9 accounts for about 20% of hepatic CYP enzyme activity and contributes to the metabolism of medications such as diazepam, imipramine, amitriptyline, and phenytoin.[42] While ethnicity plays a significant role in explaining observed interindividual variation in CYP2C9 metabolism, sex does not seem to produce any effect.[42,43]

CYP1A2

Evidence indicates that the activity of the CYP1A2 is slower in women than in men.[44,45] Tricyclics, fluvoxamine, and clozapine are all metabolized by the CYP1A2.[27,35,36] Moreover, the isozyme CYP1A2 is important for the metabolism of other drugs, such as propanolol, theophylline, and warfarin.[27,35,36] Therefore, the possibility of adverse events at the same doses of these drugs is higher in women than in men.

Further, it is noteworthy to underline that CYP1A2 is the major smoking-inducible CYP isozyme, which may account for the wide variability in the activity of the enzyme.[46] Moreover, the genetic polymorphisms of CYP1A2 predominantly affect its inducibility by smoking rather than the baseline activity.[47] When evaluating the probe substrate, caffeine,[48,49] or drugs metabolized by CYP1A2 (clozapine[50] and olanzapine[51]), some consistent findings demonstrated higher activity of CYP1A2 in men compared with women in both Caucasians and Chinese populations.

CYP3A4

The most important gender difference, however, involves the isozyme CYP3A4,[6] which represents more than 60% of the cytochrome P450.[52] This isozyme is responsible for the metabolism of several BDZs, painkillers, calcium channel blockers, and steroids.[6,21,36] The activity of this isozyme appears to be influenced both by gender and age: young women show higher levels of activity compared to both men and women of postmenopausal age.[6] Therefore, it is expected that plasma levels of BDZs will be lower in young women than in men or older women. A lower therapeutic activity of these drugs could derive from this effect in young women; moreover, the greater activity of the isozyme CYUP3A4 would determine a greater risk for abstinence after BDZs withdrawal or development of dependence (Table 4).

The hyperactivity of the CYP3A4 isozyme in women of fertile age may determine lower concentrations and, therefore, less efficacy of different drugs, such as anticonvulsants (carbamazepine) and chemotherapeutics (tamoxifene).[27]

The declining activity of CYP3A4 with age is observed more often in men than in women.[53] This effect, combined with the increased fat proportion in elderly women and decreased oxidation in elderly men, suggests that older women should have lower BDZ levels than older men at comparable doses.[54]

When examining the possible influence of sex on CYP3A4 activity, it is important to mention the possible confounding role of ethnicity, as CYP3A4 activity is higher in Caucasians than in African Americans, and in Caucasian women than in Asian women.[55]

Table 4. *Gender and age differences in cytochrome P450 activity*

Isoenzyme P450	Female gender	Senile age	Drug
CYP3A4	↑ activity	↓ activity	BDZ, nefazodone
CYP1A2	↓ activity	No effect	Fluvoxamine
CYP2C19	↑ activity	No effect	Citalopram, clomipramine

Elimination

The kidney is the major organ of drug excretion of both the parent drug compounds and metabolites. Drugs can be excreted into the urine through glomerular filtration, passive diffusion, and active secretion. Increased renal blood flow and glomerular filtration increase the elimination rate of drugs cleared by the kidneys. Sex differences have been described for glomerular filtration, tubular secretion, and tubular reabsorption, which are all faster in men.[56–59]

Pharmacodynamics

Pharmacodynamics is the study of drug mechanism of action, including the physiological and biochemical effects on the body, and the relationship between drug concentration and the rate and extent of pharmacologic response. Therefore, at any given blood concentration, a drug may show variations in response, including differences in effectiveness or safety. Pharmacodynamic data on psychotropic drugs are few in number, so available findings will be reported for each major class of compounds, together with specific pharmacokinetic characteristics, in the next several paragraphs.

Benzodiazepines

The studies exploring sex-related pharmacokinetic differences of BZDs showed that the clearance of BDZs metabolized by conjugation (lorazepam and oxazepam) are generally slower in women than in men, while that of BDZs metabolized by oxidation is identical in the two sexes.[60] Just a few data reported that the maximum concentrations of alprazolam are higher in women than in men; however this finding seems to be more related to weight differences than to sex.[61] As oral contraceptives inhibit the oxidative metabolism and facilitate the conjugation metabolism, the co-administration of BZDs with hormonal oral contraceptives needs to be considered carefully, and would suggest the need of a dose readjustment.[62]

To our knowledge, no information on pharmacodynamic differences between the two sexes for BDZs is available in the literature.

Antipsychotics

Gender-related differences in pharmacokinetics for atypical antipsychotics are demonstrated for clozapine, olanzapine, and sertindole. CYP1A2 is a major isozyme responsible for clozapine elimination, and slight differences between men and women have been shown.[63] Some findings suggest that women show higher plasma levels than men of both clozapine and its major metabolite, norclozapine,[64] but only at the beginning of the treatment.[65] The same difference has been reported also for olanzapine.[66–68]

Since blood volume is less in women, but lipid mass is greater than in men, the volume of distribution of lipophilic drugs, such as antipsychotics, is greater in women than in men. This may prolong the half-life of antipsychotics in the body with accumulation over time—a phenomenon that becomes relevant when administering depot preparations.

It is noteworthy that women are more likely than men to be taking antidepressants, mood stabilizers, pain killers, and contraceptives or hormone replacements, and these agents can interact with antipsychotics, especially those processed mainly by the CYP2D6 enzyme subsystem.

Although influenced by different factors, it is generally believed that the response to antipsychotics is more pronounced in women than in men.[69]

Recently, some studies have evaluated different incidences of the major side effects of antipsychotics, such as extrapyramidal, cardiac, sexual, and weight gain in the two sexes, but the ensuing findings are controversial. Acute dystonia, believed to be more prevalent among men, was shown to happen more often in women than men in one study only.[8] Tardive dyskinesia, generally thought to be typical of elderly women, was shown to be a risk factor, although less severe, for elderly men.[70–72]

Women show increased risk of torsades de pointes with drugs that can prolong the QT interval[73]; therefore the use of high doses of haloperidol, which prolongs this interval, in emergency situations may be especially dangerous in women.[74] For this reason, it is mandatory to perform an ECG before an injection of haloperidol.

Hyperprolactinemia is more robust in women than in men taking both typical and atypical antipsychotics.[75–77] The same is true for weight gain and related complications.[78–81]

Antidepressants

Most antidepressants are weak bases, and therefore they are more effectively absorbed under basic conditions. As already mentioned, women secrete less gastric acid, resulting in a more basic environment, which could potentially lead to enhanced absorption of antidepressants in the stomach.[82] In addition, women have a slower rate of gastric emptying than men do, thus increasing antidepressant absorption time.[83] This increase persists even after menopause, and it is enhanced by exogenous estrogens and progesterone.[83,84] As women possess a higher percentage of adipose tissue than men do, lipophilic antidepressants, in particular trazodone[85] and bupropion,[86] show a

prolonged half-life and lower plasma concentrations in women.[87,88] In contrast, a study of paroxetine in elderly patients reported the opposite findings.[89]

The peculiarities of protein binding in women make them particularly susceptible to the development of severe toxic effects by TCAs, especially when these are co-administered with other drugs that displace them from protein binding.[26]

Antidepressants are metabolized by, inhibit, and/or induce a wide range of cytochrome P450 (CYP) enzymes, as reported in the previous section.[90]

A few studies have reported sex differences in the pharmacokinetics of both TCAs and SSRIs. In women compared with men, some studies have found higher concentrations of clomipramine[91] and desmethylclomipramine,[92] but not in adolescent patients.[93]

As far as SSRIs are concerned, higher citalopram and desmethylcitalopram concentrations have been described in women than in men,[94] but only in young patients.[95] On the contrary, no differences have been detected for escitalopram,[96] sertraline,[97] and fluoxetine.[98] Higher concentrations were reported in women than in men for paroxetine in one study only,[99] and the same was true for fluvoxamine.[100] Women, compared to men, also show higher concentrations of mirtazapine and demethylmirtazapine and a longer half-life.[100]

Although there appears to be no difference in depression symptom severity, generally women respond better to SSRIs[101] than men, who, conversely, respond better to TCAs.[102–106] This may due to the fact that women produce more tryptophan and less cortisol when exposed to SSRIs.[107]

Interestingly, in two studies carried out by our research group, we noted better response of compulsive symptoms to either fluvoxamine or clomipramine in men than in women who suffer from obsessive-compulsive disorder.[108,109]

Conclusions

Both pharmacokinetic and pharmacodynamic differences between the sexes have been described that may influence psychotropic drug effects. Generally, women are characterized by lower levels of gastric acidity and lesser activity of some gastric enzymes, all of which are factors that increase drug plasma concentrations. Further, women have a reduced capacity for gastric elimination, lower body weight, lesser blood volume, and a greater percentage of fat mass compared to men. These factors are important in determining the absorption and distribution of drugs, and consequently their efficacy and tolerability. In particular, BDZs are highly lipophilic and are accumulated in the adipose tissue with a significant increase of their half-life in women, especially when elderly. Even the protein-binding capacity in plasma shows important sex-related differences, in the sense that women are characterized by a lower concentration of proteins compared to men, which leads, especially in the case of drugs that bind strongly to the proteins, such as TCAs and BDZs, to a greater risk for more severe side effects and toxicity. Women are characterized by both slower hepatic metabolic processes and reduced capacity for glomerular filtration compared to men. The diminished capacity of elimination of different compounds, compared to men, may expose women to a greater possibility of severe toxic effects. As far as the enzymatic system of the cytochrome P450 is concerned, the most important sex difference involves the CYP3A4 isozyme, which is responsible for the metabolism of several psychotropic drugs. This isozyme shows a greater level of activity in young women than in men or postmenopausal women.

Sex-related peculiarities may also account for a different sensitivity of men and women to side effects of some psychotropic drugs and may perhaps influence the drug response, but specific data on these topics are very limited.

The clinical significance of reported differences warrants some considerations. The difference in size between men and women means that translating these results to clinical dosage rates should include an adjustment for body size, which currently is not done. Reports of sex differences that persist after considering weight may warrant further dosage adjustments. It should be also underlined that investigations are often performed in healthy fasting individuals, but generally medications are prescribed to patients with confounding influences of disease, co-medications, diet, and social habits. The relative role of sex on pharmacokinetics and pharmacodynamics as compared to genetics, age, disease, social habits, and their potential interactions in the clinical setting is not yet fully known, but should be routinely considered. Therefore, although data are scattered and controversial, clinicians must be aware of a substantial impact that sex might have on efficacy and development of side effects. In our opinion, this is an exciting field of research in psychopharmacology that needs to be widely promoted in upcoming years.

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REVIEW ARTICLE

Alzheimer's disease drug development: translational neuroscience strategies

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Alzheimer's disease (AD) is an urgent public health challenge that is rapidly approaching epidemic proportions. New therapies that defer or prevent the onset, delay the decline, or improve the symptoms are urgently needed. All phase 3 drug development programs for disease-modifying agents have failed thus far. New approaches to drug development are needed. Translational neuroscience focuses on the linkages between basic neuroscience and the development of new diagnostic and therapeutic products that will improve the lives of patients or prevent the occurrence of brain disorders. Translational neuroscience includes new preclinical models that may better predict human efficacy and safety, improved clinical trial designs and outcomes that will accelerate drug development, and the use of biomarkers to more rapidly provide information regarding the effects of drugs on the underlying disease biology. Early translational research is complemented by later stage translational approaches regarding how best to use evidence to impact clinical practice and to assess the influence of new treatments on the public health. Funding of translational research is evolving with an increased emphasis on academic and NIH involvement in drug development. Translational neuroscience provides a framework for advancing development of new therapies for AD patients.

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Key words: Alzheimer's disease, clinical trials, translational research, biomarkers, omics, animal models.

FOCUS POINTS

- Alzheimer's disease (AD) is becoming more common as the world population ages.
- New treatments for AD are urgently needed.
- Translational neuroscience comprises the development of new treatments and diagnostic devices that will assist in diagnosing, preventing or treating diseases of the nervous system.
- Animal models of AD demonstrate efficacy and safety in pre-clinical settings and function as screens for agents to be advanced to human testing.
- Clinical trial programs include Phase 1 testing to establish human pharmacokinetics, Phase 2 assessments to demonstrate proof of concept and dose and Phase 3 trials to confirm efficacy.
- Biomarkers demonstrate the biological effects of disease modifying drugs and assist in AD drug development programs.
- Funding of translational research is changing with an increased emphasis on discovery in academic medical centers with support from philanthropy and advocacy groups leading to later stage in licensing by pharmaceutical companies.
- U.S. federal resources available to support AD drug development include the National Center for Advancing Translational Science (NCATS), the Clinical and Translational Science Award (CTSA) programs and the Alzheimer's Disease Cooperative Study (ADCS) among others.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that progresses from mild cognitive impairment to severe dementia and death. AD is increasingly common with age, doubling in frequency every five years after the age of 60.[1] AD is rapidly becoming a major challenge to public health, as well as a common personal catastrophe for patients and families as the world's population ages. Therapies that prevent or delay the onset, slow the progression, or improve the symptoms of AD are urgently needed. Five drugs are approved for

the treatment of AD—tacrine, donepezil, rivastigmine, galantamine, and memantine—but no agents have been approved since 2004 despite many phase 3 trials.[2] There is increasing concern about the difficulty of developing drugs with disease-modifying potential and with the high costs associated with AD drug development.[3,4]

The challenges associated with AD drug development occur in the context of shifts that are occurring in how science is organized, with an emphasis on translational research and translational medicine. Translational research is usually divided into four stages (T1–T4) that link basic science to clinical science and clinical science to the practice of medicine and public health outcomes, respectively.[5] T1 addresses the transfer of knowledge of disease mechanisms into the development of new methods for diagnosis, treatment, or prevention of disease; T2 refers to the translation of results of clinical studies into clinical practice and decision making.[5] T3 addresses diffusion and implementation in community practice, and T4 assesses real-world outcomes on public health.[6] Translational research focuses on the development of new devices, drugs, and diagnostics that will have benefit to people in the short or long term. Translational neuroscience comprises the development of new treatments and diagnostic devices that will assist in diagnosing, preventing, or treating diseases of the nervous system. Much of AD drug development is embraced by the concept of T1 translational neuroscience. Translational neuroscience includes animal models of AD, biomarkers for AD, and clinical trials for AD diagnostics and therapeutics. Translational neuroscience, when successful, leads to the development of products (drugs, devices), and there is a commercial application for this aspect of science. In this article, we address the challenges of AD drug development, how translational neuroscience approaches may be applied to AD drug development, and how financial and commercial aspects of AD drug development are integrated into the decision framework.

Alzheimer's Disease Drug Development

The first successful drug development program for AD culminated in the approval of tacrine, a cholinesterase inhibitor. Other cholinesterase inhibitors with improved safety profiles or formulations followed, with the approval of donepezil, galantamine, and rivastigmine and rivastigmine patch. Recently, high-dose options for donepezil and rivastigmine have been approved.[7,8] Memantine is an N-methyl-D-aspartate (NMDA) antagonist that was approved for the treatment of AD in 2004. No other classes of agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD.

Table 1. *Agents that completed phase 3 trials for AD and showed no drug-placebo difference on prespecified primary outcomes*

AN 1792
Atorvastatin
B6, B12, folate
Bapineuzumab
DHA
ELND005/AZD-103
Estrogen
Latrepirdine (dimebon)
Leuprolide
Naproxen
Omega-3 fatty acids
Phenserine
Prednisone
Phenserine
Rofecoxib
Rosiglitazone
Semagacestat
Solanezumab
Tarenflurbil
Tramiprosate
Valproate
Xaliproden

There have been many failures in AD drug development (Table 1). In some cases, the absence of a drug–placebo difference at the trial's end reflected failures of the trial as suggested by the absence of decline in the placebo group, excessive measurement variability, or failure to demonstrate a treatment effect in an active comparator arm of the study using donepezil.[9] In other trials, the failure of the program to lead to an approvable agent could be ascribed to lack of efficacy or safety.

Translational Neuroscience: Model and Key Concepts

Figure 1 shows the steps of drug development. The process begins and ends with human disease. Patients are identified as suffering from a disease, and study of the disease leads to targets that are possibly amenable to therapeutic manipulation to prevent or slow the disease process. Candidate therapies are identified in assays, typically by high throughput screening in which thousands to millions of compounds are screened in an assay to identify "hits" that may be developed into "leads" that may eventually be optimized into candidate therapies. These basic science steps are not necessarily included in the concept of translational research, although the quest to find assays that better predict human efficacy and toxicity

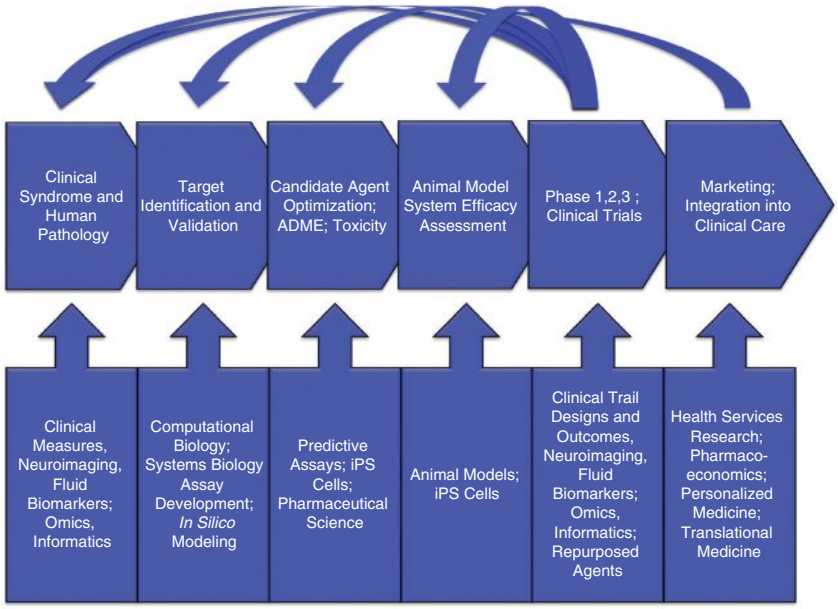

Figure 1. Overview of translational research as a framework of drug development.

blurs the boundaries between basic and early translational science. For example, *in silico* structure–activity relationship (SAR) modeling and dynamic molecular simulations are used to identify compounds for AD that are most likely to inhibit amyloid-beta aggregation and related neurotoxicity.[10] SAR modeling of c-Jun-N-terminal kinase (JNK) inhibitors has aided in identification of brain-penetrant compounds that are predicted to be more effective in preventing neurodegeneration.[11] High-content screening in intact cell lines is increasingly used to identify promising compounds, and "humanizing" this approach through the use of induced pluripotent stem cells (iPS cells) builds a physiologic bridge between the screen and human application.

Once a lead compound or group of related compounds is identified that has promise in the screening assays and has properties that support "druggability"—acceptable physical and chemical properties that suggest they might be developed as therapies—then pharmacokinetic and pharmacodynamic studies of the agents can be initiated. Pharmacokinetic studies establish the absorption, distribution, metabolism, and excretion (ADME) of the agent, and toxicity studies search for cardiac, pulmonary, liver, endocrine, renal, skin, muscular, and nervous system effects that might disqualify the agent for further study. Development of neurotherapeutic compounds in the translational neuroscience paradigm has the additional challenge posed by the need to penetrate the blood–brain barrier. Long-term carcinogenic studies and research that might indicate reproductive toxicity and teratogenicity are pursued. At least two species are assessed for most potential effects, and species known to be particularly sensitive to some adverse events (e.g., dogs in the case of cardiac effects) are employed. Again, these pharmacologic studies are not necessarily of a translational nature, but to the extent that they can be made to be more predictive of human ADME and toxicity, the more translational value this research assumes. Recent progress in predicting renal toxicity using biomarkers is an example of translational research that advances early-stage drug development.[12]

Preclinical pharmacodynamic assessment typically involves determining the effect of the candidate agent on an animal model of the disease. For AD, aged animals, senescence accelerated animals, chemical- and lesion-induced rodent models, and transgenic species (mice, rats, fruit flies, and others) comprise the animals in which testing occurs.[13] Combinations of animals and sequential testing in model systems may be more predictive of human efficacy and provide more insight into the range of effects of the agent,[14] but no animal model recapitulates all aspects of AD, and none have yet successfully anticipated a beneficial effect in subjects with AD. Readouts of the effect of the test agent include behavior (i.e., Morris Water Maze, fear conditioning, novel object recognition), histology (i.e., number of plaques), and biochemistry (i.e., total amount of amyloid beta-protein [Aß]). Dose–response relationships are explored. Improving the predictive value of animal models is a key component of translational neuroscience as applied to AD drug development. There are many aspects to this translational challenge: species-to-species relationships, timing of intervention, dose equivalency,

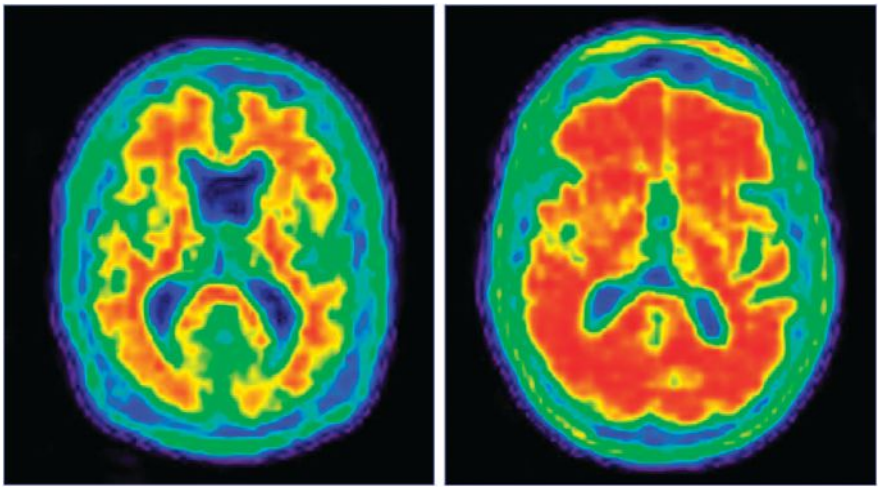

Figure 2. Florbetapir amyloid imaging in a healthy elderly person and an age-matched individual with Alzheimer's disease.

pathways affected, duration of treatment, genetic background, genetic contribution to the pathophysiology (e.g, transgenic species are humanized with known human mutations, but most patients with AD do not have a disease-causing mutation). Biomarkers applied in animals and then advanced to humans may provide necessary bridges between preclinical and clinical observations that have not yet been fully exploited. Animals models are a key element of translational research.

Once safety and efficacy have been established to an acceptable level in preclinical studies, the compound is advanced to human testing. First-in-human phase 1 studies involve testing single and multiple ascending doses beginning with doses typically 10-fold lower than the no observable adverse event level (NOAEL) in animals, adjusted to human doses by allometric scaling from the most sensitive species assessed. Human pharmacokinetics of the test agent are established in phase 1, and the maximum tolerated dose is also determined. Approximately, 50% of compounds are terminated at this point in development.[15]

Phase 2 clinical trials establish proof of concept (phase 2a) and the dose(s) (phase 2b) to be advanced to phase 3 trials. Phase 2 trials also expand the safety information available on the test agent. It is at phase 2a that there is the greatest influence of translational research. AD progresses slowly, and the sponsor is faced with the conundrum of doing a large lengthy study to establish clinical benefit or doing a shorter smaller study with a biomarker as the key outcome.[16] Biomarkers have smaller standard deviations of measurement and require smaller numbers to show drug-placebo differences.[17,18] There is substantial risk associated with this decision, since no biomarker has been proven to predict the clinical outcomes in AD trials. This is a central challenge for translational research because biomarkers are a focus of translational investigations. Biomarkers may have diagnostic value and become commercialized products of translational research (e.g., amyloid imaging with florbetapir; Figure 2), or they may be indicators of a therapeutic response used in drug development but not independently commercialized. In some cases, drugs and biomarkers are codeveloped in theranostic programs.[19]

Approximately 35% of candidate drugs are progressed from phase 2 to phase 3.[15] There is substantial controversy about how to define a phase 2 success. As noted, an effect on a biomarker may not predict a clinical response. Phase 2 outcomes that did not meet their primary endpoints may be interpreted as successful if a responsive subgroup is identified, but this strategy often results in failure to reproduce the subgroup findings in a larger trial.[20] Well-conducted phase 2 studies will facilitate better understanding of the biology and pharmacology of the candidate, and will improve phase 3 success rates by allowing those agents with promise to be advanced and those with less promise to be stopped. Extending phase 2 to better understand the pharmacology and biology of the agent will result in more phase 3 successes. Improved trial designs and outcomes assessments are an important aspect of translational research to optimize the opportunity to develop successful treatments for AD.

Phase 3 confirms the observations of phase 2 in a larger number of patients and, if successful, leads to marketing approval of the new agent. Seventy percent of agents with positive phase 3 trials are prepared for FDA review; the overall chance of an agent entering phase 1 to be shown safe and effective and advanced to FDA review is 11%, and the attrition rate is higher for central nervous system drugs than for drugs in other

therapeutic areas.[15,21] Once a new agent is available for widespread use, the later phases of translational research are inaugurated. T3 research refers to the translation of research into clinical practice, and T4 refers to the impact of the new intervention on public health.[22] Evidence-based medicine refers to the practice of medicine as informed by double-blind placebo controlled trials and other data-driven methodologies.[23]

Biomarkers in AD Drug Development

There are five primary types of biomarkers relevant to AD drug development: (1) brain imaging; (2) electrophysiologic measures; (3) plasma and cerebrospinal fluid (CSF) measures of prespecified analytes; (4) "omics" platforms with microarray and spectroscopic determination of multiple gene, protein, lipid, metabolite, or other measures combined with advanced informatics required to interpret the study results; and (5) genetics (Table 2).

Brain imaging plays an increasingly important role in AD drug development (Table 3).[24] Magnetic resonance imaging (MRI) can be used to define a trial population, assess disease modification, or follow specific types of adverse events. MRI allows structural measures of the whole brain, ventricular system, or hippocampus; investigation of functional circuit activity with functional MRI (fMRI); measurement of white matter integrity with diffusion tensor imaging (DTI); assessment of blood flow with arterial spin labeling (ASL); and interrogation of neurochemical constituents with MR spectroscopy (MRS).[25] Positron emission tomography can be used with a variety of tracers: fluorodeoxyglucose (FDG) assessing, cerebral metabolism; fibrillar amyloid demonstrating the presence of neuritic plaques; aggregated protein to establish the presence of tau and amyloid (2-(1-{6-[(2-fluorine 18-labeled fluoroethyl)methylamino]-2-napthyl}ethylidene) malonitrile [FDDNP]); 5-HT1A receptors to show receptor function and neuronal integrity; verapamil measurement of p-glycoprotein function in the blood–brain barrier; oxygen measures of oxygen extraction; and translocation protein (TSPO; also known as the peripheral benzodiazepine receptor) assessments of microglial activation.[26–31] Single-photon emission computed tomography (SPECT) offers a measure of cerebral blood flow,[32] as well as emerging measures of amyloid; dopamine transporter imaging can be used to exclude patients with dementia with Lewy bodies who have an AD-type phenotype.[33,34] MRI has played a critical role in detecting amyloid-related imaging abnormalities (ARIA) of the effusion and hemorrhagic type observed in the course of amyloid lowering clinical trials,[35,36] and is required as a safety measure in anti-amyloid treatment trials. Sample sizes required to show a drug–placebo difference with imaging are much smaller than those required to show clinical differences. For example, in a 6-month trial of an agent demonstrating a 20% drug–placebo difference in change from baseline, 257 patients would be required per arm to show the difference with ventricular atrophy, whereas 1370 would be required if the Alzheimer's Disease Assessment Scale—cognitive portion (ADAS-cog) was the outcome (these figures become 468 and 2100 for ApoE e4 noncarriers).[37] Neuroimaging is a critically important tool in translational neuroscience research for AD drug development.

Specific CSF analytes have been extensively studied in AD, including Aβ-42, total tau, and phospho-tau (p-tau). The ratio of decreased CSF Aβ-42 to elevated tau or p-tau has high sensitivity and specificity for the diagnosis of AD.[38] Production of amyloid protein

Table 2. *Biomarkers relevant to AD drug development*

Brain imaging
– Structure
○ Magnetic resonance imaging (MRI)
○ Diffusion tensor imaging (DTI: white matter tracts)
○ Cortical thickness mapping (surface based cortical thickness estimation and voxel-based morphometry approaches)
– Function
○ Fluorodeoxyglucose positron emission tomography (FDG PET)
○ Functional MRI (fMRI)
○ MRI arterial spin labeling (ASL)
○ Single photon emission computed tomography (SPECT) of cerebral blood flow
○ Dopamine transporter SPECT
– Molecular and chemical constituents
○ Amyloid PET
○ MR spectroscopy (MRS)
Electrophysiology
– Electroencephalography (EEG)
– Evoked potentials (EP)
Fluid analytes (plasma, serum, CSF)
– Amyloid-related measures (Aß40, Aß42, other Aß species)
– Inflammatory markers (cytokines)
– Oxidation markers (isoprostanes)
– Other serum and CSF measures
– Amyloid synthesis/clearance with stable isotope labeled kinetics (SILK)
Omics
– Genomics
– Transcriptomics
– Proteomics
– Metabolomics
Genetics
– Disease-related (e.g., apolipoprotein genotype)
– Pharmacogenetics (e.g., CYP enzyme genotypes)

Table 3. *Neuroimaging in AD drug development*

Patient selection

- Amyloid imaging
- Hippocampal atrophy
- FDG PET hypometabolism
- SPECT dopamine transporter imaging (to exclude dementia with Lewy bodies)

Outcomes

- Brain structure
  - MRI of whole brain atrophy
  - MRI of ventricular volume
  - MRI of hippocampal atrophy
- White matter integrity
  - MRI diffusion tensor imaging (DTI)
- Amyloid imaging
  - PET amyloid signal
  - SPECT amyloid signal
- Amyloid and tau imaging
  - FDDNP (fibrillar amyloid and aggregated tau imaging)
- Metabolic imaging
  - Cerebral metabolism (FDG PET)
  - Oxygen extraction and utilization (O-15 PET)
- Functional imaging
  - fMRI with activated imaging
  - Resting state functional connectivity of the default networks
- Cerebral blood flow imaging
  - SPECT cerebral blood flow
  - MRI arterial spin labeling
- Brain biochemistry imaging
  - MR spectroscopy
- Receptor occupancy imaging
  - 5-HT1A serotonin receptors (measure of receptor occupancy and cell survival)
- Microglial imaging
  - Microglial activation
- p-Glycoprotein function
  - Verapamil PET

Adverse event monitoring

- ARIA-E with MRI
- ARIA-H with MRI

ARIA – amyloid related imaging abnormalities; ARIA-E – effusion; ARIA-H – microhemorrhage; FDDNP – 2-(1-{6-[(2-fluorine 18-labeled fluoroethyl)methylamino]-2-napthyl}ethylidene) malonitrile; FDG – fluorodeoxyglucose; MRI – magnetic resonance imaging; MRS – magnetic resonance spectroscopy; PET – positron emission tomography; SPECT – single photon emission computed tomography.

can be assessed with stable isotope labeled kinetics (SILK).[39] Gamma secretase inhibitors have been shown to decrease Aβ production.[40] SILK presents the opportunity to test target engagement and proof of pharmacology to help decide whether to advance agents in the drug development program. This is a direct translational neuroscience role. Analytes in blood have thus far been less useful in diagnosis and drug development of AD; however, studies of the potential translational application of inflammatory, oxidative, and other serum and plasma markers are being pursued.[41,42]

Genetic studies focus on individual genes, whereas genomics refers to the entire genome or DNA sequence of organisms. Apolipoprotein E e4 is the gene variant that has the greatest impact on late-onset AD, increasing the risk of the disease and decreasing the age at onset.[43] Other genes accounting for smaller percentages of the variance of AD risk but making identifiable risk contributions include CLU, PICALM, BIN1, SORL1, and CR-1.[44,45] Some of the risk genes identified have a role in amyloid beta-protein metabolism, but genetic observations also implicate immune system function, cholesterol metabolism, and synaptic membrane processes.[46] These observations point toward new avenues of drug discovery and development.

"Omics" strategies are another important component of contemporary translational neuroscience. RNA transcription of DNA leads to transcriptomics, which includes not only a comprehensive survey of the messenger RNA, but also noncoding RNAs such as micro-RNAs, which are emerging as key regulators of gene expression in normal and disease states. Proteomics refers to the analysis of proteins as they exist in the cell, revealing aspects of protein processing and post-translational modification that cannot be inferred from the corresponding DNA sequences alone. Metabonomics (metabolomics) involves the characterization of small molecules in circulatory or cell/tissue systems, and interactomics refers to the interactions among these levels.[47,48] All these omic signatures are based on expression arrays and mass spectrometric techniques that produce profiles of up-regulated and down-regulated expression of RNA, proteins, and metabolites found in tissues and fluids (blood, saliva, CSF).[48] The metabolome includes the metabolites of molecules such as fatty acids, amino acids, nucleosides, steroids, and vitamins.[48] Proteomic studies in AD suggest prominent involvement of inflammatory cell systems that may be relevant to treatment.[49] Thus far, omic approaches have not informed drug development for AD, but these approaches promise to contribute to target identification and validation, predictive understanding of biological systems, monitoring of therapeutic responses, and eventual biological engineering.

The next step in utilizing omic data is the integrated analysis of genetic, genomic, protein, metabolite, cellular, and pathway event data into systems biology.[48] The use of advanced mathematical strategies

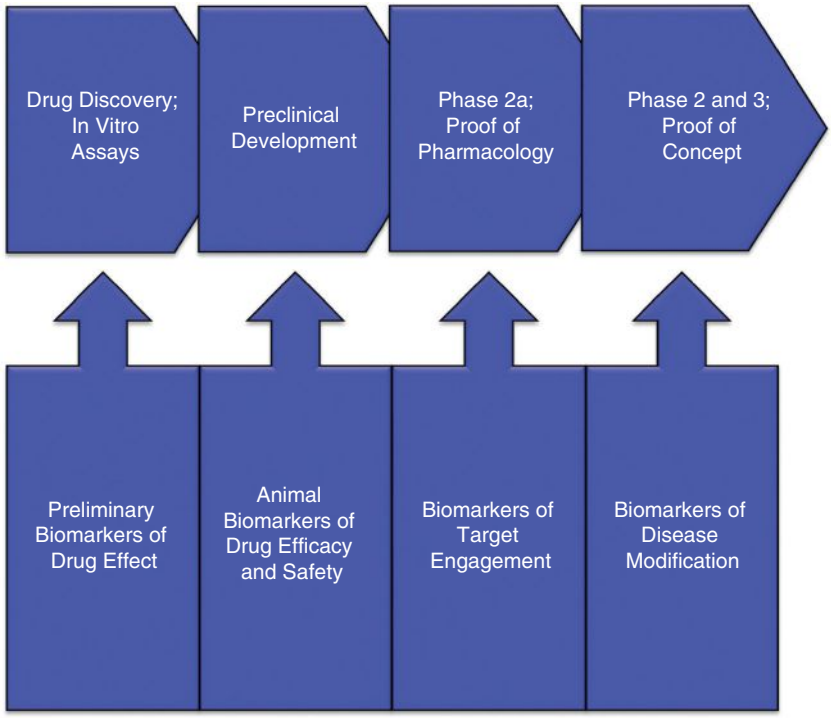

Figure 3. Role of biomarkers in drug development.

including informatics, biostatistics, data integration, computational biology, simulation and modeling, network analysis, and knowledge assembly is required to interpret the huge inventories of data generated by microarray and mass spectrometry studies.[48,50,51] This level of analysis is sometimes called quantitative biology, and systems and quantitative biology promise to become informative tools for drug discovery and development.[51] Translational informatics attempts to directly derive clinically relevant information from the vast omic data.[52]

Closely aligned with the concepts of omics and biomarkers is personalized medicine (also called precision medicine). In this approach, the unique biology of the individual patient is characterized in an effort to choose the right drug, in the right dose, for the right patient, given at the right time.[52] Pharmacogenetics and pharmacogenomics are examples of precision medicine. Second-generation omics-based medicine will be predictive and is based on a thorough grasp of the complex manifestations of the disease from which the individual suffers.[52] Omics-based medicine is increasingly providing a platform for translating quantitative systems biology into evidence-based medicine.

Biomarkers have several important roles in drug development (Figure 3).[24] They are used in drug discovery and in vitro assays to detect the effect of compounds in preliminary screens. They have important roles in preclinical drug development to detect evidence of efficacy or toxicity in animal models of the target disease. In preliminary human studies, they provide evidence of proof-of-pharmacology (POP) and target engagement (e.g., the SILK technique described above). In later stage clinical trials, they provide evidence of disease modification and proof-of-concept (POC) related to the putative mechanism of action (MOA) of the test agent. It is the hope of personalized (precision) medicine that biomarkers will eventually assist in choosing a responder and guiding dose, duration, and possible evolution of therapies over the course of the disease.

Funding Landscape for Translational Neuroscience and AD Drug Development

Translational research emphasizes products in the form of new diagnostic tests, drug treatments, devices, or processes that improve patient health through prevention or treatment. Products become available to broad populations through the processes of regulatory approval and marketing. The pathways by which the results of translational research become marketed products is being reshaped. In the traditional model, the National Institutes of Health (NIH) financed the basic science stages of idea development in academic settings, and then the product was either licensed to a company through university technology transfer offices or the inventor spun off a small

biotechnology company and tried to raise capital to advance the product through angel funding (typically supporting very early development) and venture capital. If the product continued to show promise, the biotechnology company continued to seek venture capital or eventually had an initial public offering (IPO) and became publically owned with an infusion of capital sufficient to continue to progress the product toward market. Alternatively, a company with a promising product or the biotechnology company might be purchased by a major pharmaceutical company as a means of supplying the internal product pipeline of the pharmaceutical company. The difficulty of raising funds for the late preclinical and early clinical phases of development (ADME, toxicity, early stage human trials) gave rise to the name of "valley of death" for this stage of product development.[53–55] In this model, angel funding, venture capital, biotechnology companies, and pharmaceutical companies all played critical roles in the financial ecosystem for drug and device development.

The low rate of success of drug development—especially CNS drug development—has led to marked changes in the approach to funding and more changes are anticipated. It is more difficult to attract venture capital to biotechnology endeavors, and pharmaceutical companies desire more advanced compounds and more well developed data packages before in-licensing, partnering, or purchasing a product.[56] De-risking compounds through the stage of POC or even phase 2 data is required by most pharmaceutical companies before they consider acquiring a candidate drug.

Alternative financial models are emerging. Pharmaceutical companies are working more closely with academic researchers and funding research in exchange for the right to develop products of interest.[57] This increases opportunities for academic researchers to increase their involvement in early-stage translational research, but it imposes new demands in terms of reproducibility, scalabilty, intellectual property, and conflict of interest that impact the research. Some pharmaceutical companies are also funding nonprofit research institutes—such as Calibr funded by Merck in California—that will pursue research intended eventually to feed product pipelines. States and national governments are also starting or supporting venture capital firms intended specifically to support biotech and to fill the void left by traditional capital sources.[58] New approaches to funding are emerging, such as supporting one specific part of the drug development cycle.[59]

Philanthropy can play a critical role in drug development by supporting programs that can advance a drug or product from one stage to another. Philanthropic funding tends to be limited compared to industry, venture, and federal sources. Venture philanthropies "invest" in projects and share in intellectual property ownership and licensing or milestone payments if the compound is licensed, partnered, or sold.[60] The Alzheimer Drug Discovery Foundation (ADDF) has promoted this funding model for AD drug discovery and development.[61,62]

Advocacy groups are also taking a greater role in drug development. This is particularly evident among advocacy groups for rare diseases, but AD groups also assist in drug development through programs such as the Alzheimer's Association's trial-match program and policy advocacy undertaken by the Alzheimer's Association, Alzheimer's Foundation of America, USAgainstAlzheimer's, and others.

Large clinical systems can capitalize on their high patient volume, electronic medical records, and multisite locations to support clinical trials and drug development. The Cleveland Clinic Lou Ruvo Center for Brain Health, for example, has four locations in the U.S. in an integrated trial network that can optimize AD patient recruitment and conduct of clinical trials.

The NIH is also responding to the crisis in drug development funding. The formation of the National Center for Advancing Translational Science (NCATS) is one milestone in reorganizing the NIH to orient more toward public–private partnerships and product development.[63] NCATS has resources to support drug discovery and advance promising compounds through preclinical development, including assay development and high-throughput screening, synthesis, formulation, pharmacokinetics, toxicology, medicinal chemistry, molecular libraries probe production, genomics, interference RNA, tissue chips for drug screening, and technologies for identifying and validating drug targets. The Molecular Libraries Small Molecule Repository maintains a collection of >300,000 chemically diverse compounds for use in high throughput screening projects. The Rescuing and Repurposing Drugs program supports investigation of therapeutic effects of approved or abandoned compounds for indications other than the one originally intended. NCATS programs to support clinical stage development include the Clinical Translational Science Award (CTSA) funding a network of clinical trial sites throughout the nation and the Cures Acceleration Network (CAN). The National Institutes of Neurological Disease and Stroke (NINDS) operates a "virtual pharma" model of drug development, including bioactivity/efficacy studies, medicinal chemistry, pharmacokinetics, toxicology, manufacturing and formulation development, and phase 1 clinical trials for neurotherapeutic compounds as part of its Blueprint Neurotherapeutics Network.[64] The Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD)[65,66] conducts clinical studies of neuroprotective compounds in Parkinson's disease, and the Network of Excellence in

Neuroscience Clinical Trials (NeuroNext) is a network of trial sites organized by the NINDS to test drugs in adult and pediatric populations with neurological diseases. Observations made in Parkinson's disease trials may impact other neurodegenerative disorders, including AD. The National Institute on Aging (NIA) funds AD-related drug discovery (R21 grants) and development (UO1 grants), as well as the AD Cooperative Study (ADCS), is a multisite network for AD clinical trials, and the AD Neuroimaging Initiative (ADNI), which is a public–private partnership to study biomarkers in healthy elderly, those with mild cognitive impairment (MCI), and those with mild AD.[24,67] The NIA also supports the National Alzheimer Coordinating Center (NACC), a database of standardized clinical and pathology data collected at NIA-funded Alzheimer Disease Centers.[68] The NIH Small Business Research (SBIR) funding program supports drug development in small businesses including biotechnology companies. Together, these programs provide a substantial federal resource for AD drug discovery and development. They comprise a broad platform for translational neuroscience in support of development of AD therapeutics.

Summary

The population of AD patients is rapidly expanding, and means of preventing or intervening in the disease process must be identified. Past approaches to drug development were effective in developing symptomatic agents, but they have consistently failed in the attempt to develop disease-modifying agents. New means of discovering agents and predicting human effects, better animal models, improved trial designs and outcomes, and more predictive biomarkers are needed. Translational neuroscience provides a framework for accelerating AD drug discovery and development.

Disclosures

Jeffery Cummings is a consultant for or has stocks/stock options in the following companies: ADAMAS, MedAvante, Neurokos, Neurotrax, Prana, QR, and Sonexa. He is a consultant for Abbott Laboratories, Acadia, Anavex, Astellas Pharma US, Avanir, Avid, Baxter, Bayer Healthcare, Bristol-Myers Squibb Co., Elan Pharmaceuticals, EnVivo, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Medtronic, Merck & Co, Inc., Neuronix, Otsuka Pharmaceuticals, Pain Therapeutics, Inc., Pfizer, Plexxicon, Sanofi Aventis, Signum Bioscience, Takeda, Toyama, and UBC. He performs consulting, teaching, and speaking work for Eisai, Forest Pharmaceuticals, Lundbeck, Novartis, and Ortho McNeil Janssen Scientific Affairs LLC. He owns the copyright for Neuropsychiatric Inventory. Ryan Walsh is a consultant/advisor for Lundbeck and a consultant, advisor, and member of the speaker's bureau for Teva. Kate Zhong is a consultant for Baycrest and Janssen Scientific Affairs. The remaining authors have nothing to disclose.

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REVIEW ARTICLE

Hot and cold cognition in depression

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We discuss the importance of cognitive abnormalities in unipolar depression, drawing the distinction between "hot" (emotion-laden) and "cold" (emotion-independent) cognition. "Cold" cognitive impairments are present reliably in unipolar depression, underscored by their presence in the diagnostic criteria for major depressive episodes. There is good evidence that some "cold" cognitive abnormalities do not disappear completely upon remission, and that they predict poor response to antidepressant drug treatment. However, in many studies the degree of impairment is moderately related to symptoms. We suggest that "cold" cognitive deficits in unipolar depression may in part be explicable in terms of alterations in "hot" processing, particularly on tasks that utilize feedback, on which depressed patients have been reported to exhibit a "catastrophic response to perceived failure." Other abnormalities in "hot" cognition are commonly observed on tasks utilizing emotionally valenced stimuli, with numerous studies reporting mood-congruent processing biases in depression across a range of cognitive domains. Additionally, an emerging literature indicates reliable reward and punishment processing abnormalities in depression, which are especially relevant for hard-to-treat symptoms such as anhedonia. Both emotional and reward biases are strongly influenced by manipulations of the neurochemical systems targeted by antidepressant drugs. Such a pattern of "hot" and "cold" cognitive abnormalities is consistent with our cognitive neuropsychological model of depression, which proposes central roles for cognitive abnormalities in the generation, maintenance, and treatment of depressive symptoms. Future work should examine in greater detail the role that "hot" and "cold" cognitive processes play in mediating symptomatic improvement following pharmacological, psychological, and novel brain circuit-level interventions.

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Introduction

Depression is a common, distressing, and debilitating disorder that is frequently chronic and relapsing. Common treatments include antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), which influence monoamine transmission, and psychological treatments, such as cognitive behavioral therapy (CBT), which focus on encouraging patients to challenge their dysfunctional attitudes and negative automatic thought processes. Depression is the leading cause of disability worldwide in terms of total years lost to ill health,[1] and is associated with absenteeism from work and presenteeism while at work (reduced productivity). In England in 2007, lost earnings due to depression amounted to £5.8 billion (~$8.7 billion), and it has been estimated that lower productivity accounts for a further £1.7–£2.8 billion (~$2.5–$4.2 billion).[2]

Why should clinicians be interested in cognition in depression? First, depression is a cognitive disorder, as emphasized by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV[3]) criteria for a major depressive episode (MDE). MDE Criterion 8 states that a depressed individual may have "diminished ability to think or concentrate, or indecisiveness"; MDE Criterion 2 is the cardinal symptom of anhedonia, defined as "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day"; MDE Criterion 5 includes objective psychomotor retardation. Thus, depression fundamentally alters the perception of and interaction with the environment, including the social environment, and information processing. Second, it is this cognitive impact that primarily affects the ability to function, whether in the workplace, at school, or at home. Moreover, disrupted cognition may prevent severely ill patients from deriving full benefit from psychological treatments. Third, marked cognitive impairment predicts poor response to antidepressant medication, independent of symptom severity.[4] Finally, in some

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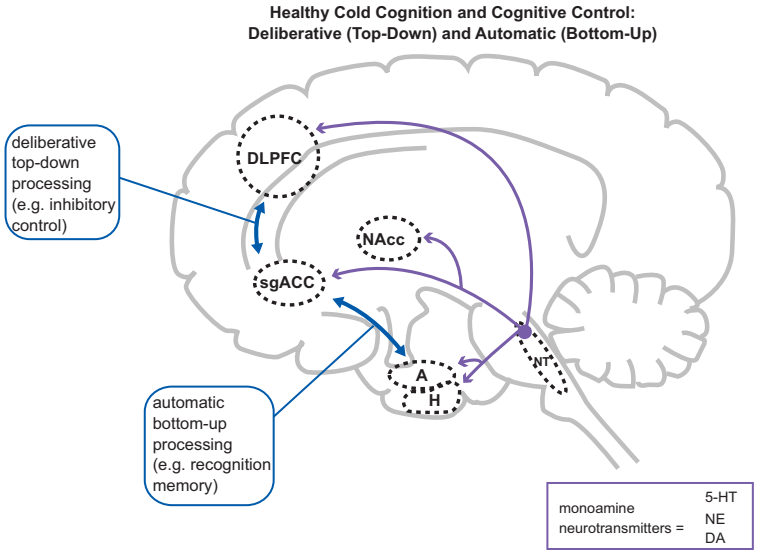

Figure 1. Normal "cold" cognition in nondepressed individuals. "Cold" (emotion-independent) cognition is instantiated via a complex set of circuits, including interactions (blue arrows) between the dorsolateral prefrontal cortex (DLPFC), the dorsal anterior cingulate cortex (ACC), and the hippocampus (H). Limbic structures connected to DLPFC, ACC, and H, such as the amygdala (A), the nucleus accumbens (NAcc), and the subgenual portion of the ACC (sgACC) also may also be activated during cold cognition, but are more strongly engaged during "hot" (emotion-laden) cognition (Figure 2). Monoamine neurotransmitter (NT) projections (purple arrows) emanating from the brainstem, including serotonin (5-HT), norepinephrine (NE), and dopamine (DA), may influence cold cognition via modulatory actions in cortical and subcortical regions. Note that most circuit nodes and connections are excluded in this and later figures for clarity, and that some connections may be indirect.

depressed patients, cognitive abnormalities may not resolve completely upon remission, and are also observed in first-degree relatives, suggesting that they may be trait markers (predisposing factors). Hence, cognitive abnormalities may serve as useful avenues of research in the search for the neurobiological underpinnings of the disorder,[5] as well as in the identification of at-risk individuals.

"Cold" Cognition in Depression

"Cold" cognition refers to information processing in the absence of any emotional influence (Figure 1). Theoretically, cold cognition is engaged on tests where the stimuli are emotionally neutral and the outcome of the test is not motivationally relevant (though motivational influences could conceivably turn a cold test "hot"; see Might "Cold" Cognition Be Turned "Hot" in Depression? below). Examples of neuropsychological tests usually considered cold include standardized pencil-and-paper assessments commonly used to assess function in neurological patients, for example the California Verbal Learning Test, the Trail-Making Test, and the Wisconsin Card Sort Test. Reliable impairments on such neuropsychological tests were observed from the 1970s onward in depressed patients. Some early studies adopted a classical neuropsychological case series approach,[6] comparing the performance of individual depressed patients against population norms, identifying deficits of a magnitude judged to be clinically significant in several patients. More frequently, case-control designs were employed, and by the mid-1990s numerous studies comparing specific cognitive measures between groups of depressed patients and comparison subjects had been reported, particularly on memory tests.

In 1995 Burt *et al.*[7] performed the first systematic review of this literature, identifying nearly 100 case-control reports examining memory performance in depressed patients. Their meta-analysis identified deficits in patients of standardized effect sizes (Cohen's d) in the range 0.27 (small) to 0.67 (medium-to-large), varying across outcome measures. Surprisingly, patients who were younger exhibited greater deficits. However, several of the studies included subjects with organic neurological illness, and did not match the groups on important demographic variables such as age and educational level, making it difficult to draw firm conclusions. A later meta-analysis by Veiel,[8] which utilized more stringent inclusion criteria, identified higher effect sizes for memory, in the range 0.83–0.97 (large), and additionally reported differences in other domains of cognitive function, with only tests in the domain "attention and concentration" apparently relatively spared in depressed patients (however, see next paragraph). This latter result does appear surprising, given Criterion 8 for an MDE: "diminished

ability to … concentrate." Importantly, impairments on paper-and-pencil tests have been observed reliably in unmedicated samples.[9]

The advent of theoretically based, computerized cognitive tests in the 1990s provided an important methodological advance in understanding cognition in depression. One example of this approach is in the use of the Cambridge Neuropsychological Test Automated Battery (CANTAB; http://www.cantab.com). Broadly consistent with the results from pencil-and-paper studies described above, impairments were noted on a wide variety of CANTAB tests, including not only memory and executive function,[10] but also attentional measures.[11] These later studies employed computerized continuous performance tests (for example the CANTAB Rapid Visual Information Processing test, RVP) to assess sustained attention, in which subjects must detect specific targets presented in a train of hundreds of successively presented stimuli, separated by a sub-second time interval, over several minutes.[11] The marked difference in results from previous studies exemplifies one advantage of utilizing a computerized testing system, which allows stimuli to be presented with greater flexibility and temporal precision than traditional paper-and-pencil assessments, thereby furnishing tests with higher cognitive specificity. Other advantages of computerized testing include automated data collection, resulting in lower inter-administrator variability, as well as standardized recording and scoring of results.

This approach contrasts with earlier non-computerized studies, in which continuous performance paradigms such as the RVP were impractical to administer routinely. As such, the only measures of attention available in the meta-analysis of Veiel[8] were variants of the digit-span test from the Wechsler Adult Intelligence Scale, which does not require a high degree of sustained concentration, and in a recent meta-analyses of executive function in depression was found to be relatively unimpaired.[12] Several studies identified cognitive impairment during remission,[13] though it is possible that some of this continued impairment might be explained in part by residual subclinical symptoms, as meta-analyses have reported small-to-moderate (r values in the range 0.1–0.5) relationships between the degree of cognitive impairment and symptom load.[14]

Later work confirmed the clinical significance of cognitive deficits during a depressive episode, at least in elderly patients (reviewed in Pimontel *et al.*[15]). For example, Potter and colleagues[4,16] reported that more cognitively impaired elderly depressed patients improved less following treatment with antidepressant medication. Executive function deficits appear to be particularly reliable predictors of poor treatment response,[17] and some studies have found that severely cognitively impaired depressed patients may benefit from psychological therapy specifically tailored to boosting problem solving.[18] This is consistent with complementary evidence from trials using the cognitive enhancer modafinil as an adjunct to SSRI treatment to improve response,[19] though the cognitive mechanisms underlying this potentially important finding remain to be clarified.

Might "Cold" Cognition Be Turned "Hot" in Depression?

The precise theoretical significance of these reliable group differences on cold cognitive measures has been a matter of debate. Some investigators interpret these effects as reflecting a core feature of depression, likely of central importance in its etiology with the potential to be used as endophenotypes in molecular genetic studies.[20] Others have wondered whether the poor performance observed might reflect a motivational deficit, caused by depressed patients treating task feedback differently to controls.[21] This latter interpretation has also received some empirical support. In a study using the CANTAB in depression, Beats *et al.*[13] identified a pattern of responding they termed "catastrophic response to perceived failure." When depressed patients made an error on a test, they were proportionately more likely than controls to make an error on the subsequent trial. This pattern was confirmed in several studies,[10,22] including one in which comparison patient groups were included, that were matched for overall performance.[21]

These studies raise the possibility that at least some of the poor performance on neuropsychological tests in depression might be due to altered "hot," ie, emotion-dependent, cognition (Figures 2 and 3). In other words, ostensibly cold cognitive tasks, especially those featuring explicit feedback, may take on an emotional quality in depressed individuals, and instead of using negative feedback to improve performance, depressed individuals may become discouraged. It is also possible that depressed individuals do not experience positive feedback as intensely as controls, further reducing the motivation to perform well. However, it is important to note that cold cognitive impairments have been observed on tests that do not feature explicit task feedback, and also in individuals who were fully recovered from depression. Therefore both hot and cold cognitive mechanisms are likely to contribute to poor neuropsychological test performance in depressed individuals (Figure 3).

"Hot" Cognition in Depression

In the past decade, several groups have reported that depressed individuals exhibit more negatively biased

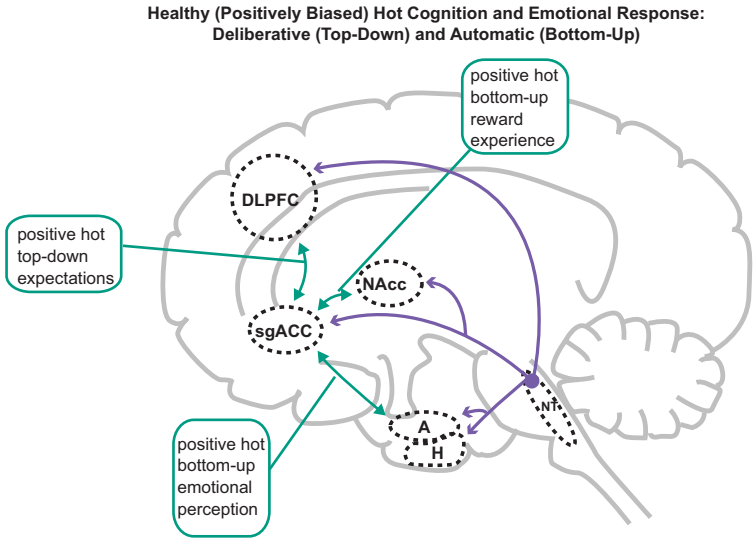

Figure 2. Normal positively biased "hot" (emotion-laden) cognition in nondepressed individuals. Hot cognition is instantiated by circuits including interactions (green arrows) between limbic regions including A, NAcc, and sgACC, the activity in which is profoundly modulated by 5-HT, NE, and DA. These regions share reciprocal connections with DLPFC, ACC, and H, and consequently hot and "cold" (emotion-independent) cognition necessarily interact (for example, motivation alters ostensibly cold cognitive test performance). Nondepressed individuals exhibit positive (green arrows) bottom-up (perceptions/experience) and top-down (expectation) biases, providing resilience to adverse events. Abbreviations and colors as in Figure 1.

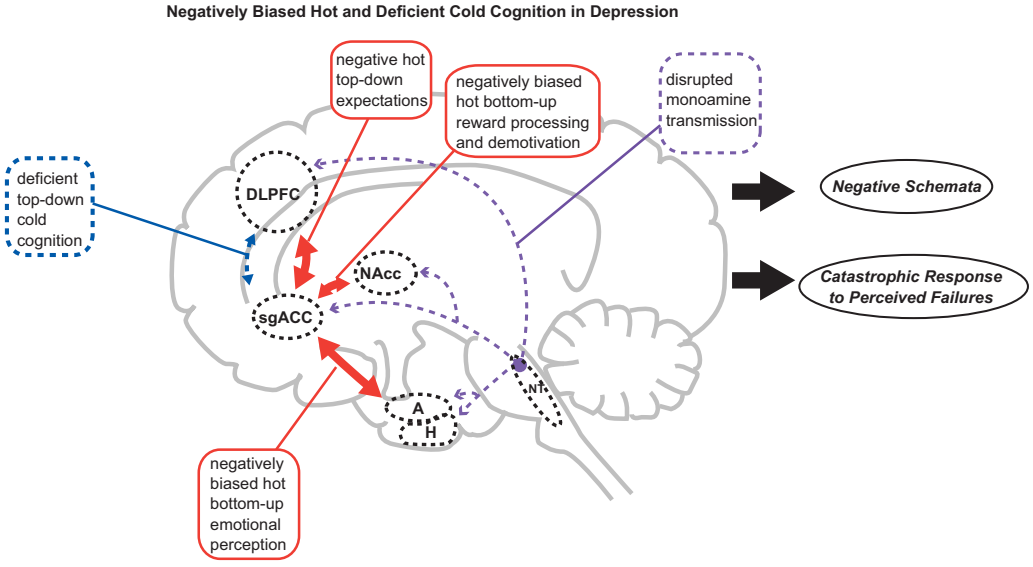

Figure 3. Negatively biased hot and impaired cold cognition in depression. Top-down cold cognitive control and monoamine transmission are both compromised (dashed arrows). Depressed individuals exhibit negative (red arrows) bottom-up biases (emotional perceptions and reward experiences) due to disrupted monoamine transmission. They also have negative top-down biases (expectations), resulting in dysfunctional and self-perpetuating negative schemata, which give rise to depressive symptoms. Abbreviations and colors as in Figure 1.

responses on tests of emotional processing. These are typically variants of cold cognitive tests that were adapted to include emotionally valenced stimuli. A common finding is that never-depressed individuals exhibit a positive bias (Figure 2), possibly reflecting resilience to negative emotional information, and that this is either attenuated or reversed in depressed individuals (Figure 3; see Roiser *et al.*[23] for a review). Such a negatively biased pattern of responding in depressed individuals, both medicated and unmedicated, has been reported on tests of perception,[24] memory,[25] attention,[26] and working memory.[27] For example, on the

CANTAB Affective Go/No-Go test, on which subjects must respond to one word-type while inhibiting responses to another, Murphy *et al.* demonstrated that while control individuals responded slightly more quickly to positive than negative target words, the converse was true for depressed patients.[28] A similar negative bias was identified using the same test in unmedicated depressed individuals.[29]

While studies of emotional bias in depression were first conducted many decades ago, abnormalities in another type of hot cognition, reward and punishment processing, have started to receive attention only relatively recently (see Eshel and Roiser[30] for a comprehensive review and studies cited therein for further details). This dearth of studies is surprising, given that anhedonia, which is closely related to reward processing, is one of the cardinal symptoms of a depressive episode. Moreover, experimental animal models of depression used for drug discovery frequently focus on behavioral constructs related to reward and punishment processing,[31] including learned helplessness, behavioral despair, sucrose preference, and intracranial self-stimulation.

Though the literature on reward processing in depression is much smaller than that on emotional biases, some consistent findings have emerged. One is the confirmation of the finding discussed above that depressed patients are hypersensitive to negative feedback[10]; this finding was determined using tasks that were designed explicitly to assess this process. During a probabilistic reward and punishment reversal learning task featuring two stimuli (one more often associated with positive feedback and the other more often associated with negative feedback), medicated depressed patients showed a pronounced tendency to switch their choice following misleading negative feedback[22]—a result that was later replicated in unmedicated patients.[32] Other studies report hypo-sensitivity to positive feedback, for example, a failure to liberalize response bias on a difficult task when more points are gained for correct responses than are lost for incorrect responses,[33] or reduced learning from rewarding stimuli.[34]

The above tasks rely on the learning of stimulus–outcome associations, while other tests have probed the impact of explicitly providing reward or punishment information about choices on decision-making in depression. One of the first studies to examine this question used the CANTAB Cambridge Gambling Task,[35] which requires participants initially to choose which of two outcomes they think will occur, with the probability of being correct varying, and then to stake points on their decision. A consistent finding across medicated, unmedicated, and even remitted samples is that depressed individuals increase their stake with increasingly better odds (termed "risk adjustment") to a lower extent than controls,[36,37] which possibly reflects ambivalence to winning points. Other studies have used effort-based tasks where subjects must respond quickly in order to achieve rewards, demonstrating reduced motivation in depression.[38] Interestingly, similar findings have been reported in subjects with schizophrenia,[39,40] who also experience anhedonia.

An important recent development in this field is the application of formal computational models to understand reward- and punishment-driven behavior. These models can dissect out specific aspects of reward processing behavior (eg, learning, points value, randomness) more precisely than analyses that use measures based on raw data.[41] For example, using such a computational approach, Chase *et al.* demonstrated that reward learning was particularly poor in highly anhedonic depressives.[42] Another recent study used computational modeling to demonstrate more random choices in subjects who scored high on depressive symptom rating scales (though without a categorical diagnosis) when using stimuli of known reward associations to guide decision making.[43]

A Cognitive Neuropsychological Model of Depression

What are the theoretical implications of hot and cold cognitive abnormalities in depression? In our view, they mandate a reframing of the classic cognitive model of depression proposed by Beck,[44] which proposes that depression results from stable, self-reinforcing, dysfunctional negative schemata, and is the inspiration for talking therapy approaches such as CBT. Beck's cognitive model predicts the presence of abnormal hot processing in depression (ie, negative emotional biases) on the basis of "top-down" influences, or what we conceptualize as "negative expectations" (Figure 3). In other words, depressed individuals may exhibit slower responses to happy words[29] or misinterpret facial expressions as sad[24] precisely because they expect to encounter such negative information in the environment. These negative expectations, which include dysfunctional attitudes and negative attributional styles, and give rise to thought processes characteristic of depression, such as negative automatic thoughts and rumination, can be considered a form of "top-down" hot cognition (Figure 3). They are the targets of psychological interventions such as cognitive therapy, which could be conceptualized as training depressed individuals to exert cold cognitive control over their top-down negative biases, for example through working memory, inhibition, and problem solving (Figure 4).

However, a complementary view that has gained convincing empirical support over the past decade is

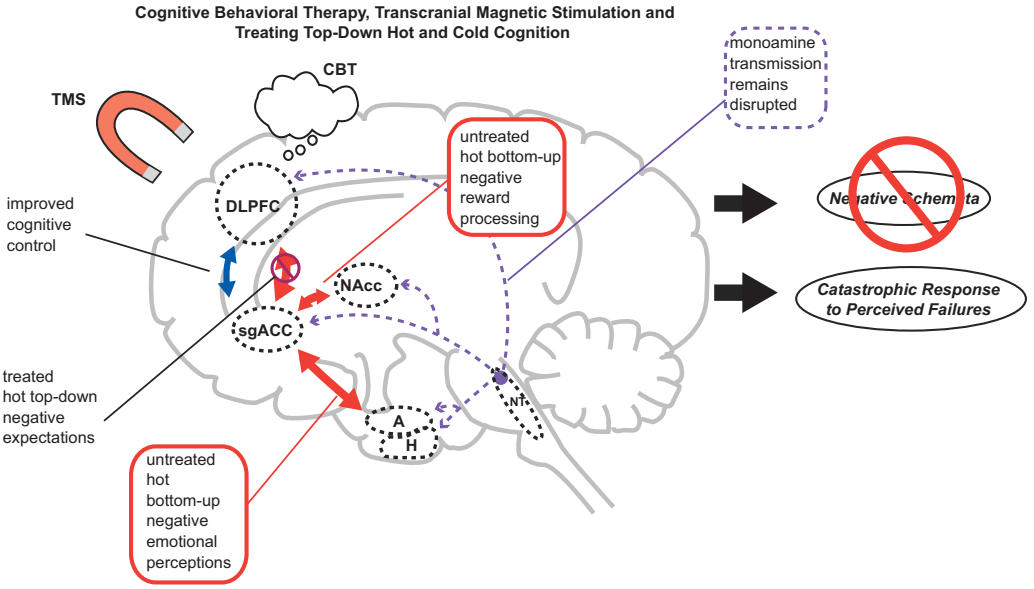

Figure 4. Treating hot and cold top-down cognition in depression. Psychotherapies such as cognitive behavioral therapy (CBT) train patients to challenge their top-down hot biases (negative expectations) and thereby resolve dysfunctional negative schemata. Transcranial magnetic stimulation (TMS) directly activates DLPFC and interconnected structures, improving cold top-down cognitive control and emotional regulation. However, dysfunctional monoamine transmission and bottom-up negative biases (negative perceptions) are not treated directly by CBT or TMS, and may thus persist. Abbreviations and colors as in Figure 1.

that disrupted neurotransmission in systems targeted by antidepressant drugs, such as serotonin, norepinephrine, and dopamine, alters the "bottom-up" processing of emotional stimuli, instantiating "negative perceptions" (Figure 3). Importantly, a large body of evidence suggests that manipulating monoamine transmission experimentally can alter reward and emotional processing biases, in both healthy volunteers and depressed individuals[45–47] (Figure 5). According to this view, negative biases occur due to compromised monoamine modulation of the neural circuits that process emotional stimuli.[48]

Our cognitive neuropsychological model of depression[23] (Figure 6) proposes an integrated approach, accommodating both the traditional psychological framework (Figure 4) and more recent psychopharmacological findings (Figure 5). We propose that bottom-up biases (negative perceptions), caused by disrupted monoamine transmission, play a causal role in the development of dysfunctional negative schemata, but that the latter can themselves engender top-down biases (negative expectations), thus maintaining negative schemata. This model also proposes a central role for a type of top-down cold cognition, cognitive control, in depression, suggesting that negative perceptions may feed into dysfunctional negative schemata particularly when cognitive control is impaired (Figure 3). Importantly, these different cognitive processes (negative perceptions, negative expectations, and cognitive control) are likely instantiated via the dysfunctional operation of separate, but interacting, neural circuits (Figures 1–3). Being able to identify signals from and manipulate these circuits may enable researchers to better parse the mechanistic heterogeneity of depression, and provide novel approaches to treatment (Figures 4 and 5).

Understanding Novel Treatments Through Cognition

The findings reviewed in this article, together with associated neuroimaging results, provide an important basis for the understanding of two novel brain circuit-based intervention strategies in treatment-resistant depression. First, repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is a non-invasive method of stimulation, by which a neural circuit implicated in cognitive control can be manipulated directly. Although rTMS for depression was first attempted in the early 1990s (see George *et al.*[49] for a review), the most convincing evidence for efficacy has come from two large double-blind trials,[50,51] both of which reported that in treatment-resistant patients, 2–3 times as many subjects who were administered active stimulation remitted (~15%) compared to those receiving sham stimulation.

The mechanisms underpinning rTMS in the treatment of depression remain to be completely clarified, but

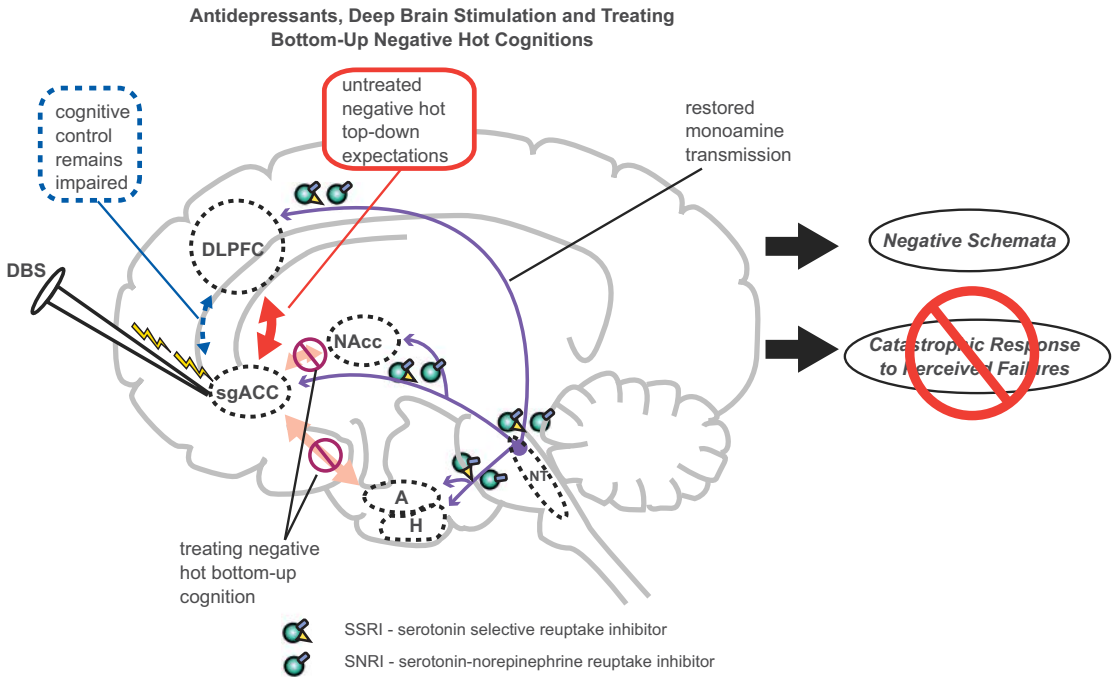

Figure 5. Treating hot bottom-up cognition in depression. Antidepressant medications target the monoamine systems (5-HT, NE, and DA), which may be disrupted in some depressed patients, thereby resolving bottom-up hot biases (negative perceptions). Deep brain stimulation (DBS) in the sgACC may influence circuits instantiating bottom-up negative biases directly, via connections with other regions in limbic circuits such as A. However, top-down negative biases (negative expectations) are not treated directly by antidepressant medications or DBS, and may thus persist. Abbreviations and colors as in Figure 1.

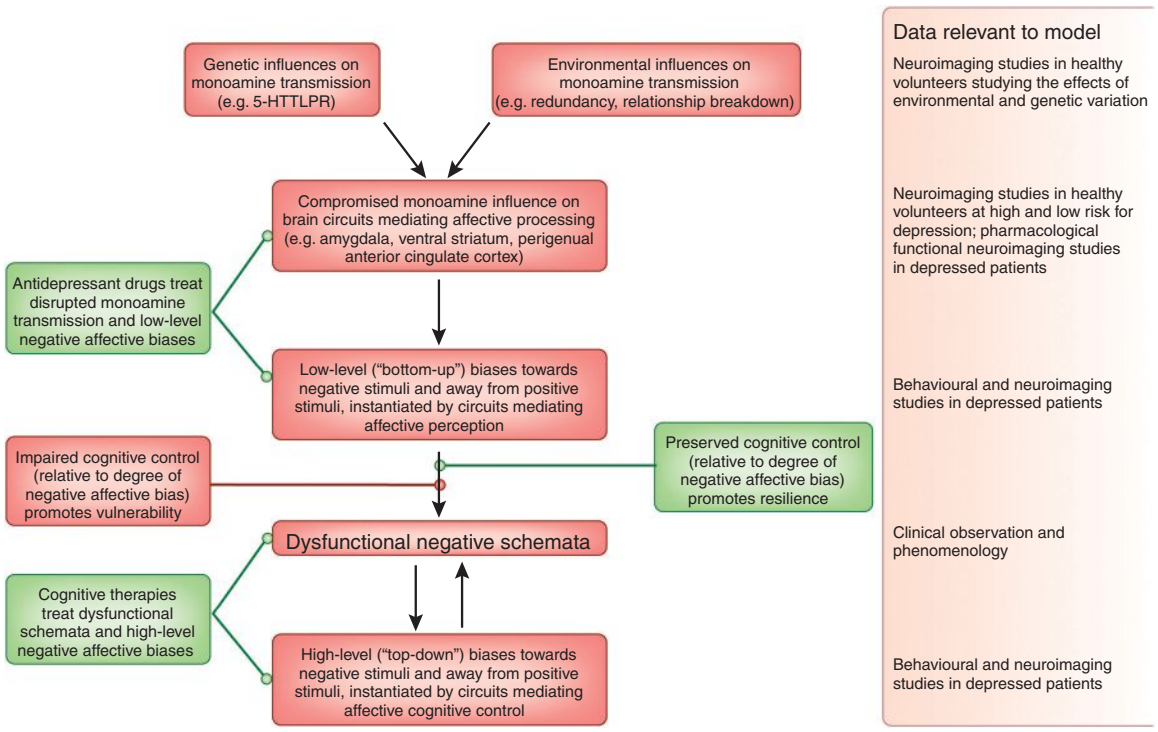

Figure 6. A cognitive neuropsychological model of depression. Red boxes/text indicate factors contributing to the development and maintenance of depressive symptoms. Green boxes/text indicate factors contributing to the treatment of and recovery from depression. 5-HTTLPR: serotonin transporter linked polymorphic region. Reprinted from Roiser *et al.*[23] with permission.

may relate to top-down cold cognition—specifically cognitive control—and its interaction with top-down hot cognition[23] (Figure 4). Several neuroimaging studies have found that depressed subjects exhibit exaggerated prefrontal cortex responses during difficult working memory tasks, interpreted as reflecting prefrontal "inefficiency," which is not altered by SSRI treatment.[52] By contrast, rTMS to the DLPFC has been reported to boost performance on tests requiring cognitive control in depressed subjects,[53] and to improve cognitive control over distracting negative information in healthy volunteers.[54] Some preliminary studies have linked these effects to symptomatic relief directly, reporting that treatment-resistant depressed patients who respond to two weeks of rTMS exhibit improved attentional control over neutral information after a single stimulation session,[55] when mood effects were not yet apparent, and that treatment response is associated with better inhibition of negative distracting information after 10 days of treatment,[56] when symptoms had started to remit. Future studies should explore in greater detail whether rTMS exerts its beneficial effects in depression by boosting cognitive control.

Second, for highly treatment-resistant depressed patients, invasive deep brain stimulation (DBS), particularly to the subgenual anterior cingulate cortex (sgACC), has been found to be effective in open-label trials.[57] The rationale for targeting this brain region is the reliable finding from neuroimaging studies that it is over-active in depressed individuals[58] and increases in metabolism during negative mood.[59] The sgACC plays an important role in hot cognition and regulates activity in the amygdala,[60] in which responses to negative stimuli are exaggerated in depression and normalized with SSRI treatment[61] (Figures 3 and 5). Importantly, responses to negative stimuli in the sgACC are blunted in both depressed patients[62] and healthy individuals at genetic risk for depression,[63] thus supporting its role in the instantiation of emotional biases. As with rTMS, the mechanism underlying the beneficial effects of DBS is not completely clear, but may be related to resolving negative bottom-up biases (Figure 5) via altered activity in the sgACC and other interconnected regions, for example the amygdala and orbitofrontal cortex.[57] Future studies should test directly whether stimulation in this region alters bottom-up negative biases in depression.

Conclusion

We have reviewed evidence that supports a central role for both hot (emotion-laden) and cold (emotion-independent) cognition in the pathophysiology and treatment of depression. Depressed patients exhibit reliable impairments on cold neuropsychological tests, and the presence of such impairments during remission suggests that these are not simply epiphenomena of illness. In the domain of hot cognition, negative emotional and reward biases are commonly reported in depression, and the finding that these can be altered by pharmacological intervention suggests that they result from bottom-up, as well as top-down, influences. However, hot and cold cognition are by no means independent, and there is good evidence for heightened responses to negative feedback in depression, which may impair performance on ostensibly cold cognitive tasks. Specifically, informative negative feedback may take on a highly emotive quality, and positive feedback may fail to exert an appropriate motivational influence in depressed patients, thus influencing task performance. Such negative feedback biases may play a particularly important role in disrupting functioning in the workplace or at school.

Our neuropsychological model of depression (Figure 6)[23] provides an integrated account of disrupted hot and cold cognition in depression (Figure 3). It also has implications for understanding common treatments such as psychotherapy and medication. For example, SSRIs may assist patients toward the goal of recovery by resolving bottom-up negative biases (Figure 5), but this goal may only be achieved if they use that assistance to work to improve their cognitive and functional outcome by challenging top-down biases (Figure 4), as suggested by the superior treatment efficacy of combined psychotherapy and antidepressant medication relative to each in isolation.[64] In other words, good mental health is an active process, and we should encourage patients to understand that they may have to work to get better, even while taking antidepressants.

Future studies should focus on the early detection of abnormalities in hot cognition,[65] since 75% of mental health disorders start before the age of 24.[66] This would facilitate earlier treatment or even prevention of depression, stopping it from becoming a lifelong disorder and robbing people of their mental capacity and well-being.[67] As a society, we know that we have to work to maintain our physical health by making an effort to eat healthily and exercise, and these messages are reinforced from the start of our formal education. Our view is that society and governments should consider good brain health in exactly the same way.

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"Meta-guidelines" for the management of patients with schizophrenia

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Guidelines for treating various conditions can be helpful in setting practice standards, but the presence of several sets of guidelines from different countries, experts, and settings, written at different times, can also create confusion. Here we provide a "guideline of guidelines" for the treatment of schizophrenia, or "meta-guidelines," which not only reconcile the various existing standards but also update them to include the use of several newer agents, most of which were marketed following the publication of existing standards.

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Key words: Assessment, acute, maintenance, antipsychotics, depot.

Introduction

Managing patients with schizophrenia can be challenging, even for the most experienced of clinicians. Over the past decade, numerous experts in various countries have made recommendations in a number of published guidelines.[1–8] In addition, many institutions and hospitals have their own unpublished versions of guidelines for how to treat patients with schizophrenia. Often these recommendations contradict one another and are quickly out of date as the ever-increasing influx of new data accumulate and novel therapeutic agents are made available. In the "meta-guidelines" presented here, we have collected recommendations from various sources, both published and unpublished, and have updated and reconciled the differences from the Patient Outcomes Research Team (PORT), the Texas Medication Algorithm Project (TMAP), the American Psychiatric Association (APA), various state and federal hospitals, and current experts with decades of experience in treating this patient population in order to create an up-to-date "guideline of guidelines." These meta-guidelines have also been extensively reviewed by a number of anonymous peer reviewers. The goal was to create a comprehensive yet concise set of meta-guidelines that reflects all the current data in order to provide clinicians with an aid in the management of patients with schizophrenia at different stages of illness, including acute and maintenance phases. Although clinical judgment must be exercised in the care of individual patients, these meta-guidelines may serve to assist clinicians in choosing the most evidence-based and up-to-date strategies for addressing treatment selection, medication-induced side effects, treatment nonadherence, and other issues commonly encountered in treating patients with schizophrenia. These meta-guidelines are intended for rank-and-file patients with schizophrenia who are not violent, self-harming, or complicated by various comorbidities, as such patients are excluded from most evidence-based randomized controlled efficacy trials that are the basis of both previously published guidelines and also of the meta-guidelines provided here.[1–8] We will provide separate meta-guidelines for more complex, yet commonly encountered patients with schizophrenia, for use and guidance for what to do when the meta-guidelines provided here fail to provide adequate outcomes.[9–14] The meta-guidelines are presented here as Tables 1–15 and Figure 1.

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Table 1. *Overview and key points*

- Consider other psychiatric disorders in making a differential diagnosis
- Form and engage in a therapeutic alliance and encourage a supportive social network in order to improve long-term outcomes
- Reassess frequently, especially if a definitive diagnosis cannot be made or if diagnosis was made in the last 12 months
- Actively monitor for and treat comorbid conditions, including substance abuse
- Integrate treatments from multiple clinicians especially for comorbid conditions
- For first-episode schizophrenia, initiate treatment with atypical antipsychotics in lower doses
- Reserve conventional antipsychotics for use only after at least one unsuccessful trial with an atypical antipsychotic
- Strongly consider clozapine after two unsuccessful antipsychotic trials

Table 2. *Assessment*

- Evaluate causes for psychotic episode
- Interview individuals close to the patient if feasible
- Verify the diagnosis
- Complete psychiatric and general medical history and status
- Identify comorbid psychiatric and medical conditions
  - Substance use (eg, marijuana)
  - Infectious diseases (eg, syphilis, HIV)
- Evaluate general medical health
- Evaluate suicide risk
- Assess likelihood for dangerous, impulsive or aggressive behavior
- Identify patient strengths and limitations
- Assess baseline values that may be affected by antipsychotic treatment
  - Vital signs
  - Weight, height, body mass index (BMI), waist circumference
  - Extrapyramidal symptoms
  - Tardive dyskinesia (AIMS)
  - Cognition (MMSE)
  - Diabetes risk factors
  - Hyperprolactinemia
  - Lipid panel
  - ECG and serum potassium and magnesium
  - Ocular exam
  - Screen for changes in vision
  - Pregnancy and sexually transmitted disease (STD)
- Consider brain imaging for patients with a new onset of psychosis or atypical clinical presentation
- Engage in therapeutic alliance

Table 3. *Suggested physical and laboratory assessments to monitor physical status and detect concomitant physical conditions in patients with schizophrenia*

Assessment	Initial or baseline	Follow-up
Vital signs	Pulse, blood pressure, temperature	Pulse, blood pressure, temperature, every visit when possible and always as clinically indicated, particularly as medication doses are titrated
Body weight and height	Body weight, height, and calculate BMI; waist circumference when possible	BMI every visit for 6 months after changing antipsychotic medications and at least quarterly thereafter for outpatients; monthly for inpatients
Hematology	CBC	Weekly for clozapine-treated patients, and decrease intervals as appropriate; whenever indicated for other antipsychotics, when clinically indicated, and when considering possibility of neutropenia

Table 3. Continued

Assessment	Initial or baseline	Follow-up
Blood chemistries	Renal function tests (BUN/creatinine ratio) Liver function tests Thyroid function tests Electrolytes Lipid panel (see Table 4)	As clinically indicated
Infectious diseases	Test for syphilis Tests for hepatitis C and HIV	As clinically indicated
Pregnancy	Consider pregnancy test for women of childbearing potential	
Toxicology	Drug toxicology screen, heavy metal screen, if clinically indicated	Drug toxicology screen, if clinically indicated
Imaging/EEG	EEG, brain imaging (CT or MRI, with MRI being preferred), if clinically indicated	

Table 4. *Suggested physical and laboratory assessments to monitor possible treatment-induced side effects in patients with schizophrenia*

Assessment	Initial or baseline	Follow-up
Diabetes	Screening for diabetes risk factors; fasting blood glucose	Fasting blood glucose or hemoglobin a1c at no longer than 4 months after initiating a new treatment and annually thereafter for outpatients; more frequently (monthly to quarterly) for inpatients depending on the agent (with high-risk agents such as clozapine and olanzapine assessed more frequently)
Hyperlipidemia	Lipid panel	At least semi-annually, and more frequently for high risk agents such as clozapine and olanzapine
Triglycerides	Assessed monthly for the first 3 months	Assess annually once treatment is stabilized or more frequently for high-risk agents
Suspected congenital QTc prolongation (family history of fainting or early sudden death)	ECG and serum potassium and magnesium before treatment with thioridazine or pimozide; ECG before treatment with chlorpromazine, ziprasidone, or iloperidone in the presence of cardiac risk factors or concomitant QT-prolonging medications	ECG with significant change in dose of thioridazine, pimozide, and, in the presence of cardiac risk factors for ziprasidone, iloperidone, or addition of other medications (eg, chlorpromazine) that can affect QTc interval; annually for other patients
Hyperprolactinemia	Screening for clinical symptoms of hyperprolactinemia	Screening for symptoms of hyperprolactinemia at each visit until stable, then yearly if treated with an antipsychotic known to increase prolactin
	Prolactin level, if indicated on the basis of clinical history	Prolactin level, if indicated on the basis of clinical history
Extrapyramidal side effects, including akathisia	Clinical assessment of extrapyramidal side effects (dystonia and Parkinsonism)	Clinical assessment of extrapyramidal side effects weekly during acute treatment until antipsychotic dose is stable for at least 2 weeks, then at each clinical visit during stable phase

Table 4. Continued

Assessment	Initial or baseline	Follow-up
Tardive dyskinesia	Clinical assessment of abnormal involuntary movements [abnormal involuntary movement scale (AIMS), or similar scale]	Clinical assessment of abnormal involuntary movements every 6 months in patients taking conventional antipsychotics and every 12 months in those taking atypical antipsychotics In patients at increased risk, assessment should be done every 3 months with treatment using conventional antipsychotics and every 6 months with treatment using atypical antipsychotics
Cataracts	Clinical history to assess for changes in distance vision or blurred vision	Annual clinical history to assess for visual changes; ocular examination with visual acuity, cataract screening, and glaucoma screening recommended every 2 years for patients under age 40 and every year for patients over age 40
Therapeutic drug monitoring	Clinical assessment of drug serum levels to ensure they are within therapeutic range	Re-evaluation of serum drug levels, especially in cases where optimal drug efficacy is not obtained or medications known to alter levels are added

Table 5. *Treatment*

Setting and housing

• Hospitalize patients:
  ○ Who pose a threat to self or others
  ○ Who are unable to care for themselves
  ○ Who need constant supervision
  ○ For whom outpatient treatment is unsafe or ineffective
• Day or partial hospitalization, home care, family crisis therapy, crisis residential care, and assertive community treatment:
  ○ For patients who do not need formal hospitalization
  ○ Patients may be moved from one level of care to another as needed

Table 6. *Treatment plan*

- Formulate and implement a treatment plan
  - Identify treatment targets and use objective outcome measures to determine effectiveness of treatment
  - Set realistic expectations for what constitutes successful treatment
  - Use objective quantitative rating scales to monitor clinical status [eg, Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Negative Symptoms Assessment (NSA)]
- Develop a treatment alliance and promote treatment adherence
  - Relate patient's individual goals to treatment outcomes
  - Assess and address factors that affect adherence
    - Side effects
    - Lack of insight
    - Patient perception of medication risks and benefits
    - Cognitive/memory impairments
    - Therapeutic alliance
    - Financial, transportation, and other practical barriers
    - Cultural beliefs
    - Social support
  - Consider assertive outreach
- Provide patient and family education
  - Nature of the illness
  - Signs of relapse
  - Coping strategies

Table 6. Continued

- Treat comorbid conditions including nicotine dependence and other substance use disorders
  - Pharmacological treatments for alcohol abuse
  - Substance abuse rehabilitation programs
  - Nicotine replacement therapies
  - Bupropion (use with caution; may activate psychosis or be diverted for abuse)
  - Psychosocial interventions
- Ensure that services are coordinated
- Integrate treatments from multiple clinicians
- Document treatment over the course of illness

Table 7. *Acute-phase treatment*

- Reduce stressful environmental factors
- Educate patient
  - Nature and management of illness
- Establish relationship with patient's family
  - Refer family members to the National Alliance for the Mentally Ill (NAMI) (http://www.nami.org)
- Use of antipsychotics
  - Initiate treatment as soon as possible
  - Discuss medication risks and benefits with patient and obtain patient consent whenever possible
  - Minimize side effects
  - Select medication based on:
    - ➢ Severity of symptoms
    - ➢ Prior degree of symptom response
    - ➢ Prior experience of side effects
    - ➢ Dosing convenience (eg, once daily)
    - ➢ Side effect profile of medication
    - ➢ Patient's preference
    - ➢ Available formulation

    Note: Antipsychotics tend to have the same efficacy for positive symptoms in population-based studies.
  - Titrate as quickly as tolerated to the target therapeutic dose
  - If the patient is not improving, assess for:
    - ➢ Medication nonadherence
    - ➢ Rapid medication metabolism
    - ➢ Poor medication absorption
    - ➢ Consider measuring medication plasma concentration

    Note: If the patient has adequate medication plasma concentration but is not responding to treatment, raise dose or switch medications.
- Recommendations for acute-phase treatment
  - Rapid emergency treatments for acutely psychotic patients showing aggressive behaviors:
    - ➢ Short-acting parenteral antipsychotic with or without parenteral benzodiazepine and with or without a parenteral anticholinergic
    - ➢ Rapidly dissolving oral formulations or oral concentrates of atypical antipsychotics
  - Use atypical antipsychotics as first-line treatment
    - ➢ Atypical antipsychotics may have superior efficacy for treating cognitive, negative, and affective symptoms
    - ➢ Use lower doses in first-episode individuals because they are more sensitive to extrapyramidal side effects (EPS) and metabolic side effects
    - ➢ For some patients, conventional antipsychotics may be first choice

    Note: Conventional antipsychotics may be as effective as atypical antipsychotics for acute phase treatment.
  - Clozapine should be used in patients with persistent suicidality, violence, or substance abuse

  Note: Clozapine tends to be underutilized in some treatment settings, or utilized later than recommended (ie, following multiple antipsychotic treatment failures rather than just two or three)
  - Clozapine augmentation with an atypical or a conventional agent or electroconvulsive therapy (ECT) should be preceded by a treatment-refractory evaluation including:
    - ➢ Clozapine serum levels
    - ➢ Re-examining diagnosis
    - ➢ Substance abuse
    - ➢ Treatment adherence
    - ➢ Psychosocial stressors

    Note: Clozapine may also be superior for treatment-resistant symptoms.

Table 7. Continued

- Use long-acting injectable formulations of initial oral medication for patients with adherence issues, violent behavior, or even in early-onset schizophrenia
- Adjunctive medications in the acute phase
  - For comorbid conditions
    - Major depression

    Note: Some antidepressants may sustain or exacerbate psychotic symptoms
    - Other comorbidities
  - For certain symptom domains
    - Agitation
    - Aggression
    - Affective symptoms
    - Other symptoms

    Note: Benzodiazepines may be helpful for anxiety and agitation, particularly short-term, but monitor for dependence or abuse; also reported to increase mortality with long-term use
    - Mood stabilizers and beta-blockers may be useful for hostility and aggression
  - For sleep disturbances
  - For EPS, especially dystonia and Parkinsonism
    - For prophylactic treatment of EPS, consider:
      - Propensity of the antipsychotic to cause EPS
      - Patient preference
      - Patient's history of EPS
      - Other risk factors for EPS
      - Risk factors for and consequences of anticholinergic side effects
    - Consider lowering antipsychotic dose or switching to a different antipsychotic
  - For patients with persistent severe psychosis or suicidal ideation
    - Add electroconvulsive therapy (ECT) in the acute phase
- Special issues in the treatment of first-episode patients
  - Careful documentation of symptoms, which may evolve over time
  - Predictors of poor treatment response
    - Male gender
    - Prenatal or perinatal injury
    - Early onset
    - Severe hallucinations and delusions
    - Attentional impairments
    - Lack of affective component
    - Poor premorbid functioning
    - Longer duration of untreated psychosis
    - Development of EPS
    - Distressing emotional environment
  - Attempt to minimize risk of relapse in remitted patients
  - Alleviate exposure to cannabinoids and psychostimulants
  - Enhance stress management
  - Maintenance antipsychotic treatment
  - Patient education
    - Factors that increase relapse risk
    - Indefinite antipsychotic maintenance treatment
    - Medication discontinuation with close follow-up and a plan of antipsychotic reinstitution with symptom recurrence
  - Consider using a long-acting depot formulation
- Dosing
  - Many drugs dosed higher in practice than in clinical trials (eg, olanzapine, quetiapine, paliperidone ER, ziprasidone; see Tables 11 and 12)
  - Higher dosing for multi-episode patients
  - Maintenance doses lower than acute treatment doses
  - Lower doses in elderly and children
- Adequate treatment trial
  - Wait a minimum of 3 weeks and maximum of 6 weeks before making a major change to the treatment regimen
  - In patients showing a partial response, extend trial duration to 4–10 weeks

Table 8. *Stabilization phase treatment*

- Monitor medication response and dose for the next 6 months
- Assess adverse effects and adjust medication as needed to minimize them
- Continue psychotherapeutic interventions
- Patient and family education
  - Course and outcome of illness
  - Importance of treatment adherence
  - Realistic goal setting
- Arrange for continuity of care by assuring linkage of services between hospital and community treatment before the patient is discharged from the hospital

Table 9. *Stable phase treatment*

- Ongoing monitoring and assessment
  - EPS at each clinical visit
    - ➢ Abnormal involuntary movements
      - ✓ Every 6 months for patients taking conventional antipsychotics
      Note: Every 3 months for patients at increased risk
      - ✓ Every 12 months for patients taking atypical antipsychotics
      Note: Every 6 months for patients at increased risk
    - ➢ Weight and calculate BMI; waist circumference when possible
      - ✓ Every 3 months; quarterly thereafter for outpatients; monthly for inpatients
  - Triglycerides monthly in patients at high risk for metabolic complications or on high risk agents such as clozapine or olanzapine
  - Fasting glucose and glycosylated hemoglobin a1c at 3 months then annually for outpatients and low-risk antipsychotics; more frequently for inpatients and with high-risk agents
  - Electrolytes, renal, liver, and thyroid function annually
  - Vital signs, CBC, ECG; prolactin when clinically indicated (see Tables 3 and 4 for frequency)
  - Where feasible, maintain an alliance with individuals who are likely to notice resurgence of symptoms in the patient
- Psychosocial treatments in the stable phase
  - Select appropriate psychosocial treatments based on the patient's needs
    - ➢ Family interventions
    - ➢ Supported employment
    - ➢ Assertive community treatment (ACT)
    - ➢ Social skills training
    - ➢ Cognitive behavior therapy (CBT)
    - ➢ Weight management
    - ➢ Cognitive remediation
    - ➢ Peer support and peer-delivered services
    - ➢ Combined psychosocial interventions
- Antipsychotics in the stable phase
  - Administer conventional antipsychotics at a dose close to the EPS threshold
  - Atypical antipsychotics can usually be administered at doses that are therapeutic without inducing EPS
  - Weigh advantages of decreasing antipsychotic dose against risk of relapse
  - Differentiate between increasing agitation and akathisia
  - Evaluate negative symptoms
    - ➢ Secondary to Parkinsonian syndrome?
    - ➢ Untreated major depression?
    - ➢ Anticholinergics or other sedating agents?
- Adjunctive medications in the stable phase
  - Add psychotropic medications in order to:
    - ➢ Treat comorbid conditions
    - ➢ Treat aggression
    - ➢ Treat anxiety and other mood symptoms
    - ➢ Augment antipsychotic effects of the primary medication
    - ➢ Treat side effects
  - Weight management
    - ➢ Metformin
    - ➢ Topiramate

Table 9. Continued

- Use of ECT in the stable phase
  - Maintenance ECT may be useful
    - ➢ In patients who responded to acute ECT treatment
    - ➢ When pharmacologic prophylaxis is ineffective or intolerable
- Encourage patient to use self-help treatment organizations

Table 10. *Treatment in special circumstances*

- Treatment-resistant patients
  - Assess for adequate dose and treatment adherence
  - Consider clozapine
    - ➢ For patients with an inadequate response to 2 antipsychotics (at least one of which is an atypical antipsychotic)
    - ➢ For patients with persistent suicidality
  - Augmentation with another antipsychotic, anticonvulsant, or a benzodiazepine
  - Electroconvulsive therapy (ECT)
  - Cognitive remediation therapy (CRT)
  - Cognitive behavior therapy (CBT)
- Negative symptoms
  - Assess for factors that may contribute to negative symptoms
    - ➢ Treat with antipsychotics if secondary to positive symptoms
    - ➢ Treat with antidepressants if secondary to depression
    - ➢ Treat with anxiolytics if secondary to anxiety
    - ➢ Treat with antiparkinsonian agents or antipsychotic dose reduction if secondary to EPS
  - If negative symptoms are primary
    - ➢ Consider treatment with clozapine or other atypical antipsychotics
  - Adjunctive treatment for negative symptoms
    - ➢ SSRI, SNRI, or another antipsychotic
- Relapse
  - When taking oral antipsychotic
    - ➢ Switch to a different oral antipsychotic or increase dose of the current antipsychotic
  - If treatment nonadherence is suspected
    - ➢ Switch to a depot atypical antipsychotic
    - ➢ Switch to a depot conventional antipsychotic
- When taking a depot antipsychotic
  - ➢ Switch from depot conventional to depot atypical antipsychotic
  - ➢ Increase dose or frequency of injections
  - ➢ Supplement with oral formulation of the same antipsychotic until steady state is reached

Table 11. *Commonly used medications: conventional antipsychotics*

Medication *(brand)*	Recommended dose range (mg/day)*	Chlorpromazine equivalents (mg/day)**	Half-life (hours)
Phenothiazines			
Chlorpromazine *(Thorazine)*	300–1000	100	6
Fluphenazine *(Prolixin)*	6–20	2	33
Perphenazine *(Trilafon)*	12–64	10	10
Trifluoperazine *(Stelazine)*	15–50	5	34
Butyrophenone			
Haloperidol *(Haldol, Serenace)*	6–40*	2	21

**higher doses especially when failing to respond to doses up to 20 mg*

Table 11. Continued

Medication *(brand)*	Recommended dose range (mg/day)*	Chlorpromazine equivalents (mg/day)**	Half-life (hours)
Others			
Loxapine *(Loxitane)*	30–100	10	4
Thiothixene *(Navane)*	15–50	5	34

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

**Chlorpromazine equivalents represent the approximate dose equivalent to 100 mg of chlorpromazine (relative potency).

Table 12. *Commonly used medications: atypical antipsychotics*

Medication *(brand)*	Recommended dose range (mg/day)*	Half-life (hours)	Drug interactions*
Aripiprazole *(Abilify)*	10–30	75	Half dose with strong CYP3A4 or CYP2D6 inhibitors Double dose with CYP3A4 inducers
Asenapine *(Saphris)*	10–20	13–39	Cautiously approach coadministration with fluvoxamine and paroxetine; sublingual administration without food or drink for 10 minutes after administration
Clozapine *(Clozaril)*	150–600 (FDA max 900 mg)	12	Cautiously approach coadministration with drugs that involve CYP1A2, CYP2D6, and CYP3A4
Iloperidone *(Fanapt)*	12–24	18–33	Half dose with strong CYP2D6 and CYP3A4 inhibitors Half dose in poor metabolizers of CYP2D6
Lurasidone *(Latuda)*	40–160	18–31	Not recommended with strong CYP3A4 inhibitors or inducers Reduce dose with moderate CYP3A4 inhibitors; give after ≥350 calorie snack or meal
Olanzapine *(Zyprexa)*	10–30* *some settings allow 40 mg or more for difficult cases	33	Dose adjustment may be required with carbamazepine, fluvoxamine, fluoxetine, omeprazole, and rifampin
Paliperidone ER *(Invega)*	3–12	23	Dose adjustment may be required with carbamazepine and divalproex sodium
Quetiapine *(Seroquel, SeroquelXR)*	300–750* *some settings allow 1200 mg or more for difficult cases	6	A decrease in dose may be required with CYP3A and CYP2D6 inhibitors An increase in dose may be required with hepatic enzyme inducers such as carbamazepine, phenytoin, barbiturates, rifampicin, sulphonylureas, griseofulvin, and excess alcohol
Risperidone *(Risperdal)*	2–8	24	Dose adjustment may be required with cimetidine, ranitidine, clozapine, fluoxetine, paroxetine, carbamazepine, and other known enzyme inducers
Ziprasidone *(Geodon)*	80–160* *some settings allow up to 320 mg for difficult cases	7	Dose adjustment may be required with CYP3A4 inhibitors and inducers; give after ≥500 calorie snack or meal

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

Table 13. *Commonly used medications: other*

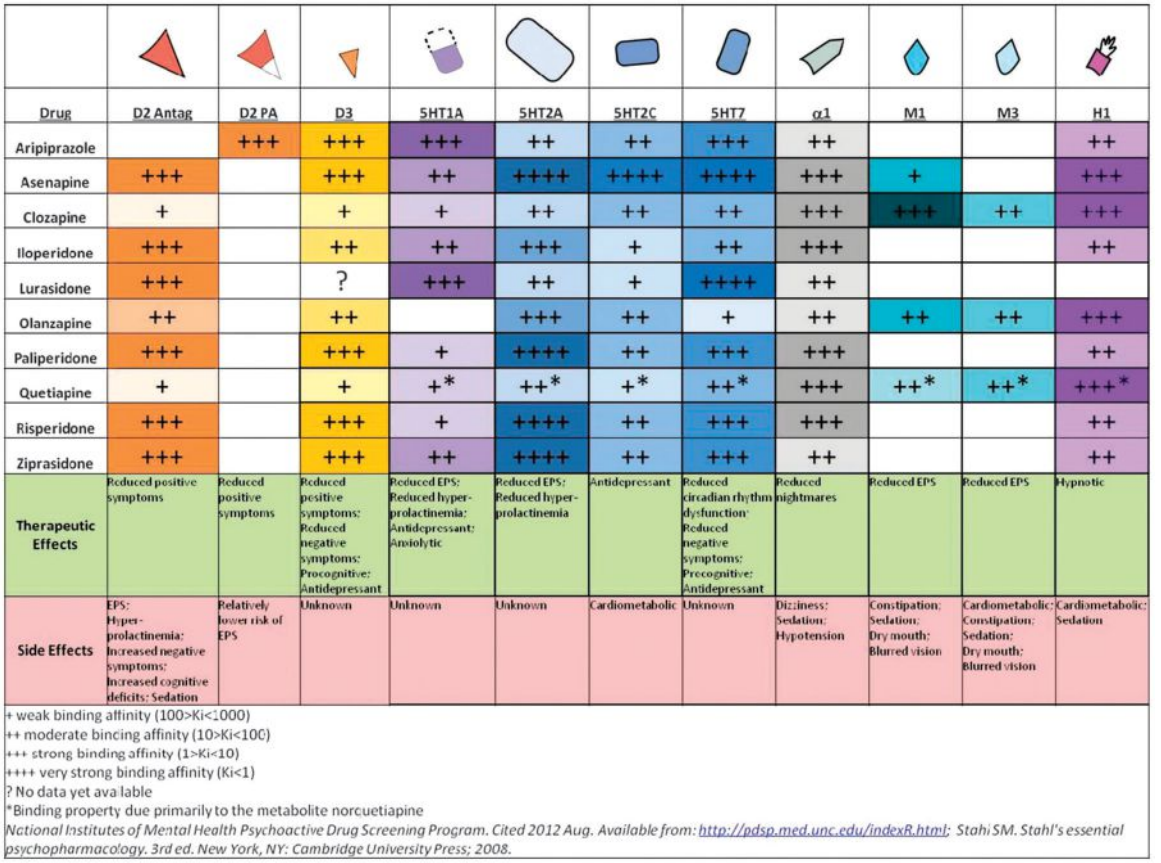
Medication *(brand)*	Recommended dose range*	Uses
Bupropion *(Wellbutrin)*	150–450 mg/day	Major depressive disorder, seasonal affective disorder, weight loss, smoking cessation. Issues include abuse potential, 2D6 inhibition
Benzodiazepines	Various	Agitation, insomnia, akathisia, anxiety
Benztropine *(Cogentin, generic)*	0.5–6 mg/day	Parkinsonism, EPS
Beta-blockers	Various	Akathisia, impulsivity, aggression
Carbamazepine *(Tegretol, generic)*	400–1200 mg/day	Seizures, mania, violence, treatment-resistant psychosis. Enzyme induction, 3A4, may significantly lower some antipsychotic levels
Diphenhydramine (*Benadryl*)	25–300 mg/day	Insomnia, EPS, EPS prophylaxis
Divalproex *(Depakote, DepakoteER, generic)*	Various	Seizures, mania, migraine prophylaxis, violence, treatment-resistant psychosis
Lamotrigine *(Lamictal, generic)*	Various	Seizures, bipolar depression, treatment resistant psychosis
Lithium *(Eskalith, generic)*	900–1800 mg/day	Mania
Metformin *(Fortamet, Glumetza, generic)*	1000–2000 mg/day	Diabetes mellitus, prophylaxis of weight gain
Oxcarbazepine *(Trileptal, generic)*	1200–2400 mg/day	Seizures, bipolar disorder
SNRIs	Various	Major depressive disorder, anxiety, chronic neuropathic pain
SSRIs	Various	Major depressive disorder, anxiety, obsessive compulsive disorder
Topiramate *(Topamax)*	200–400 mg/day	Partial onset or primary generalized tonic-clonic seizures Migraine prophylaxis, weight loss Not for treatment of mania
Trazodone *(Oleptro, Desyrel, generic)*	25–600 mg/day	Insomnia, depression at higher doses
Trihexyphenidyl *(Artane, generic)*	1–15 mg/day	Parkinsonism, EPS
Zolpidem *(Ambien)*	5–10 mg/day	Insomnia

*Dose range recommendations are adapted from the 2009 Schizophrenia Patient Outcome Research Team recommendations.[5–8] See full prescribing information for details.

Table 14. *Choice of medication in the acute phase of schizophrenia*

Patient profile	Atypical agents	Clozapine	Conventional agents	Long-acting injectables
First episode	Yes			Yes
Persistent suicidal ideation or behavior		Yes		Yes
Persistent hostility and aggressive behavior		Yes		Yes
Tardive dyskinesia	Yes, all atypical antipsychotics may not be equal in their lower or non-tardive dyskinesia liability	Yes		
History of sensitivity to extrapyramidal side effects	Yes, except risperidone			
History of sensitivity to prolactin-related side effects	Yes, except risperidone or paliperidone			
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia	Ziprasidone, lurasidone, asenapine, paliperidone ER, iloperidone, or aripiprazole			
Repeated nonadherence to pharmacological treatment				Yes

Table 15. *Receptor-binding profiles of atypical antipsychotics*



Drug	D2 Antag	D2 PA	D3	5HT1A	5HT2A	5HT2C	5HT7	α1	M1	M3	H1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	+		+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms: Reduced negative symptoms: Procognitive: Antidepressant	Reduced EPS: Reduced hyperprolactinemia: Antidepressant: Anxiolytic	Reduced EPS: Reduced hyperprolactinemia	Antidepressant	Reduced circadian rhythm dysfunction: Reduced negative symptoms: Procognitive: Antidepressant	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS: Hyperprolactinemia: Increased negative symptoms: Increased cognitive deficits: Sedation	Relatively lower risk of EPS	Unknown	Unknown	Unknown	Cardiometabolic	Unknown	Dizziness: Sedation: Hypotension	Constipation: Sedation: Dry mouth: Blurred vision	Cardiometabolic: Constipation: Sedation: Dry mouth: Blurred vision	Cardiometabolic: Sedation

+ weak binding affinity (100>Ki<1000)
++ moderate bincing affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet ava lable
*Binding property due primarily to the metabolite norcuetiapine
National Institutes of Mental Health Psychoactive Drug Screening Program. Cited 2012 Aug. Available from: http://pdsp.med.unc.edu/indexR.html; Stahl SM. Stahl's essential psychopharmacology. 3rd ed. New York, NY: Cambridge University Press; 2008.

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CBC, complete blood count; CBT, cognitive behavioral therapy; CRT, cognitive remediation therapy; CT, computerized tomography; ECG, electrocardiogram; ECT, electroconvulsive therapy; EEG, electroencephalogram; EPS, extrapyramidal symptoms; MRI, magnetic resonance imaging; NMS, neuroleptic malignant syndrome; SNRI, serotonin norepinephrine re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor.

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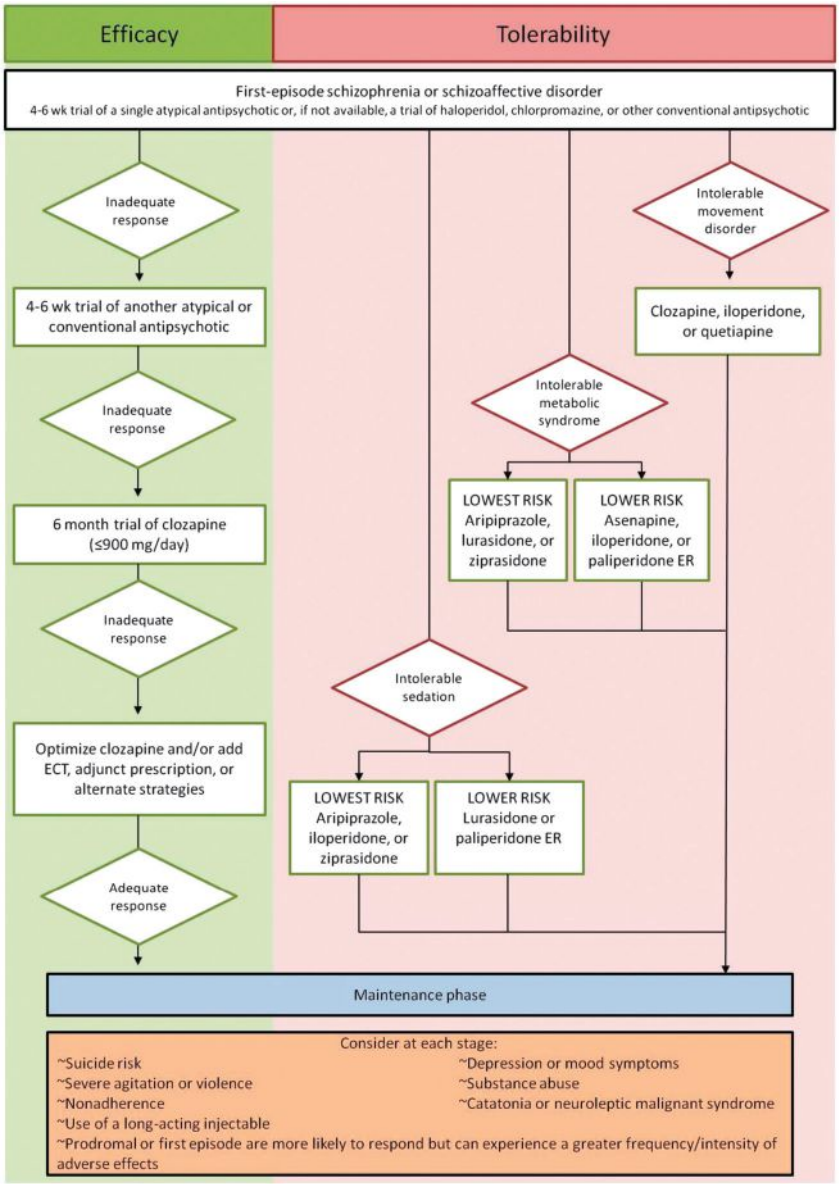

Figure 1. Antipsychotic algorithm for schizophrenia. For many acute inpatient settings with limited lengths of stay, trials of antipsychotics may be only 2–3 weeks prior to trying another. Many clinicians do not proceed to clozapine at all or until multiple failures with other antipsychotics; clozapine can be underutilized when this is the case. Response is generally defined as a clinically significant reduction in symptoms, eg, a modest 20% reduction in Positive and Negative Symptom Scale (PANSS) score observed at 2 weeks can predict a more robust 40% decrease in PANSS at 6 months. Lack of any response at 2 weeks is discouraging and requires reevaluation, including compliance and pharmacokinetics/therapeutic drug levels.

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ORIGINAL RESEARCH

A pooled analysis of six month comparative efficacy and tolerability in four randomized clinical trials: agomelatine versus escitalopram, fluoxetine, and sertraline

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Objective. A pooled-analysis on the long-term outcome in four head-to-head studies: agomelatine versus fluoxetine, sertraline, and (twice) escitalopram.

Method. A meta-analytic approach was used. Hamilton Depression Rating Scale (HAM-D) scores, response and remission rates, Clinical Global Impression of Improvement (CGI-I) scores, response and remission rates, and completion rates/discontinuation rates due to adverse events were analyzed.

Results. At the last post-baseline assessment on the 24-week treatment period, the final HAM-D-17 score was significantly lower in patients treated with agomelatine than in patients treated with selective serotonin reuptake inhibitors (SSRIs), as well in the total group of patients with severe depression (P = 0.014 and 0.040, respectively). HAM-D response rates at the end of 24 weeks were significantly higher in patients treated with agomelatine than in patients treated with SSRIs, as well in the total group of patients with severe depression (P = 0.031 and 0.048, respectively). HAM-D remission rates at the end of 24 weeks were numerically but not significantly higher in patients treated with agomelatine than in patients treated with SSRIs. Final CGI-I scores were significantly lower for agomelatine. CGI-I response as well as remission rates were numerically higher in patients treated with agomelatine, without statistical significance. The percentage of patients with at least one emergent adverse event leading to treatment discontinuation was 9.4% in patients treated with SSRIs and 6.6% in patients treated with agomelatine (P = 0.065).

Conclusion. The present pooled analysis shows that, from a clinical point of view, agomelatine is at least as efficacious as the investigated SSRIs with a trend to fewer discontinuations due to adverse events.

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Key words: Antidepressants, agomelatine, escitalopram, fluoxetine, sertraline.

Clinical Implications

- At 6 months of treatment, agomelatine has statistically significant superiority over the investigated SSRIs on the HAM-D scores, on HAM-D response rates and on CGI-I scores but the difference does not reach statistical significance for HAM-D remission rates, and for CGI-I response or CGI-I remission rates.
- At 6 months of treatment, agomelatine shows a trend to better adherence compared to the investigated SSRIs.

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Introduction

The efficacy of antidepressants in patients with major depression has been investigated in over 1000 randomized clinical trials (RCTs). One meta-analysis of 182 trials reported response rates of 53.8% for antidepressants and of 37.3% for placebo.[1] Recently, several articles were published that expressed criticism on the efficacy of antidepressants because of publication and reporting bias, and because of the relatively small effect sizes for antidepressants.[2–4] The same methodological issues are also found in trials that have investigated the efficacy of psychotherapy in depression.[5,6] Although major guidelines recommend treatment of major depression for (at least) 6–9 months after

remission, most RCTs are limited to acute phase trials of 6–8 weeks, comparing the efficacy of an antidepressant versus placebo. The knowledge on the long-term efficacy of antidepressants is mainly based on relapse or recurrence prevention studies with a placebo substitution design, ie, patients are treated open-label with active medication, and treatment responders are then randomized to continue with medication or switch to placebo in a double-blind manner.[7]

The comparative efficacy of different antidepressants has been less frequently investigated, although several meta-analysis results have been published, eg, between one antidepressant and active comparators,[8,9] between two different classes of antidepressants,[10] or between many individual antidepressants,[11] suggesting small but sometimes significant differences between drugs. One representative example showing this difference is a meta-analysis that found response rates to be 4.3% higher in patients treated with serotonin-norepinephrine reuptake inhibitors (SNRIs) than in patients treated with selective serotonin reuptake inhibitors (SSRIs).[10]

But again, most of these studies were acute phase trials. Long-term RCT data comparing two antidepressants are scarce and are most often based on an extension design, where patients are randomized to two different antidepressants during the acute phase and where the two treatments are then continued for 24 weeks.

Most of these studies are performed in psychiatric outpatients, with inclusion and exclusion criteria bringing into question the ecological validity of RCTs, but some of the small differences in acute phase trials (such as a slight superiority of venlafaxine versus citalopram, fluoxetine, paroxetine, and sertraline) have recently been (partially) replicated in a more naturalistic primary care setting during a 6-month trial (a randomized, open-label, rater-blinded study). While no significant differences were found on the primary endpoint (remission rates at 6 months), most secondary endpoints showed a slight but significant superiority of venlafaxine over the other antidepressants.[11]

Agomelatine is an antidepressant with melatonergic (MT1 and MT2) agonistic and 5-HT_{2C} antagonistic properties, with significant short-term efficacy relative to placebo, as well as evidence of relapse prevention (up to 10 months).[12] Four short-term, head-to-head, comparative studies where agomelatine was compared with fluoxetine, with sertraline, and (twice) with escitalopram, respectively, have been published.[13–16] In each of these studies, an extension phase was available up to 6 months of total treatment.

The present manuscript reports the results of the meta-analysis on the long-term outcome of agomelatine versus SSRIs in these four studies, reporting on efficacy, completion rates, tolerability, and safety.

Materials and Methods

The present meta-analysis is based on results from these 4 studies with identical design where the acute-phase, head-to-head study had an extension phase up to 24 weeks.[13–16] Patient demographics and disease characteristics are listed in Table 1.

Studies included in the analysis had the following characteristics:

- Two-arm, head-to-head, double-blind, randomized studies comparing the agomelatine and SSRIs, in non-elderly adult outpatients fulfilling DSM-IV-TR criteria for major depressive disorder (MDD), where 6 months of treatment was planned for all patients, and where the pivotal depression efficacy scale was the 17-item Hamilton Depression Rating

Table 1. *Patients' demographics and disease characteristics at baseline—FAS*

		Agomelatine N = 627	SSRI N = 635
Age (year)	Mean ± SD	42.5 ± 11.6	43.1 ± 11.4
	Min–max	18–76	18–79
Gender	Female (%)	74.2	71.7
MDD	Recurrent*	68.5%	68.1%
Number of episodes including the current one			
	Mean ± SD	2.7 ± 2.1	2.7 ± 2.5
	Median	2.0	2.0
Duration of the current episode (months)			
	Mean ± SD	5.3 ± 6.6	4.8 ± 4.1
	Median	3.7	3.1
HAM-D total score	Mean ± SD	27.2 ± 3.0	27.3 ± 2.9
CGI-S score	Mean ± SD	4.8 ± 0.6	4.8 ± 0.6

*Information not collected in the study 056.

Scale (HAM-D17) and the comparison of efficacy was specified in the protocol.

- These 4 studies had an entry HAM-D17 score of ≥22 (moderate to severe), except for one study in which HAM-D17 score was ≥25 (severe).[13] All the studies were performed in accordance with the ethical principles laid out in the Declaration of Helsinki (1964) and its text revisions applicable at the time, and were approved by relevant local ethics committees. All patients had given written informed consent.
- The pivotal short period in the individual studies varied; 6 weeks versus escitalopram[15] and sertraline,[14] 8 weeks versus fluoxetine,[13] and 12 weeks in the second study versus escitalopram.[16] The long-term depression efficacy analysis in each individual study was at 24 weeks of treatment. A dose increase (agomelatine: from 25 to 50 mg; fluoxetine: from 20 to 40 mg; sertraline: from 50 to 100 mg; escitalopram: from 10 to 20 mg) was noted in 24.8% of patients treated with agomelatine and in 22.4% of patients treated with SSRIs. Data from the four studies were pooled.
- Efficacy was examined with the HAM-D 17 score [response (a decrease of at least 50% from baseline) and remission (HAM-D total score below or equal to 6 points)] and with the Clinical Global Impression of Improvement (CGI-I) score [response (CGI-I of 1 or 2, much or very much improved) and remission (CGI-I of 1, very much improved)] using the last observation carried forward (LOCF) analysis at 24 weeks. The subgroup of severely depressed patients (baseline HAM-D17 total score of 25 or more) was also analyzed.
- The safety data were derived from spontaneous reporting of adverse events during studies, and were analyzed as the number and percentage of patients with at least one emergent adverse event (EAE) leading to study drug discontinuation. The number of patients with abnormal liver function tests (3 times above the upper limit of normal) in each group was analyzed.

Statistics

The meta-analytic method provided an estimate of the overall average treatment effect based on the individual effect of treatment compared to SSRI estimated in the four studies. The difference between agomelatine and SSRI was estimated for each study based on the last post-baseline value of HAM-D total score on the 6-months treatment period (LOCF approach) using an analysis of covariance adjusted for baseline and center (as random effect).

The homogeneity of the treatment effect across studies was analyzed based on the estimation of a difference between treatments in each study. Moreover, a test of heterogeneity in the treatment effect across the studies was also carried out.

The overall treatment effect compared with SSRI was estimated using a random effects model, which is appropriate in case of homogeneity of treatment effects between studies and in case of quantitative heterogeneity. The same meta-analytic method was used on the CGI-I score, and on response and remission defined by the HAM-D and CGI-I, to provide additional estimates of the overall treatment effect of agomelatine and its accuracy as compared to SSRIs. For those meta-analyses, unadjusted estimates of treatment effect in each individual study were used.

The safety analyses were performed in the safety set (SS) in the pool of the four studies and consisted of patients having received at least one dose of the studied treatment (636 patients on agomelatine and 648 patients on SSRIs). Type I error was set at 5% two sided for all analyses.

Results

Efficacy

Hamilton Depression Rating Scale

The HAM-D-17 score at the last post-baseline assessment on the 24-week treatment period was significantly lower in patients treated with agomelatine than in patients treated with SSRIs. The overall estimate of the difference was 1.08 (0.44) points ($P = 0.014$) in the full analysis set of patients (FAS) and 1.01 (0.50) points ($P = 0.040$) in the subgroup of patients with severe depression (baseline HAM-D ≥ 25) (Figure 1).

HAM-D response rates at the end of 24 weeks were significantly higher in patients treated with agomelatine than in patients treated with SSRIs. The overall estimate of the difference was 5.09% (2.36) ($P = 0.031$) in the FAS and 5.11% (2.59) ($P = 0.048$) in the subgroup of patients with severe depression (Figure 2). At the end of 24 weeks, response rates in the individual studies were 78.95%, 76.00%, 76.47%, and 82.61% for agomelatine, while for the SSRIs they were 74.32% (fluoxetine), 63.46% (sertraline), 73.77% (escitalopram), and 81.25% (escitalopram) in the FAS.

HAM-D remission rates at the end of 24 weeks were numerically but not significantly higher in patients treated with agomelatine than in patients treated with SSRIs. The overall estimate of the difference was 4.12% (2.79) ($P = 0.139$) in the FAS and 2.29% (3.07) ($P = 0.445$) in the subgroup of patients with severe depression (Figure 3). At the end of 24 weeks, remission rates in the individual studies were 51.42%, 55.33%, 47.06%, and 65.84% for agomelatine, while for the

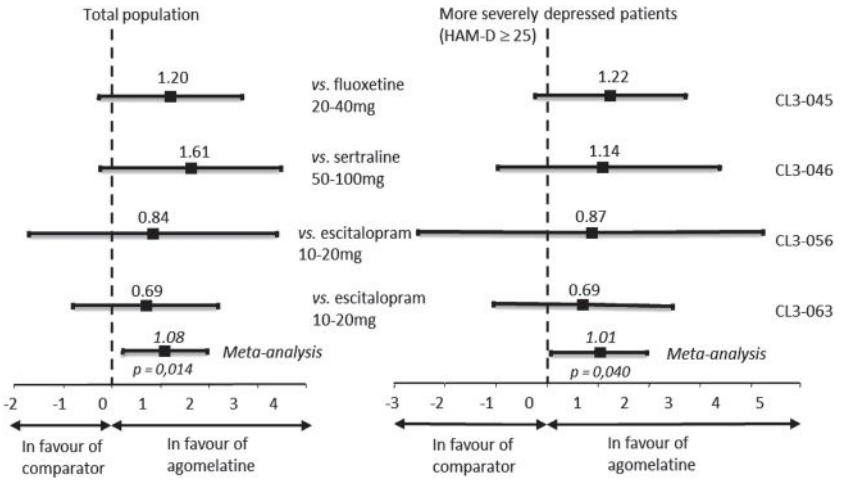

Figure 1. Long-term efficacy of agomelatine versus SSRIs in all patients and in the subgroup of more severe patients (final HAM-D-17 scores).

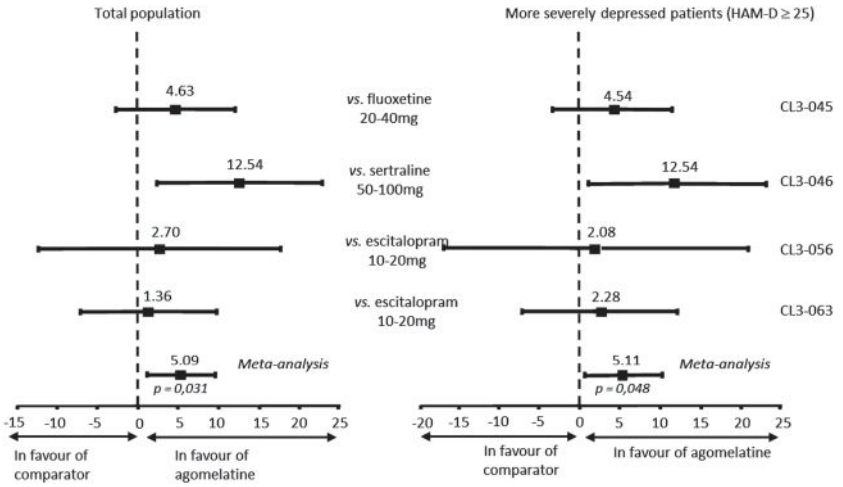

Figure 2. Long-term efficacy of agomelatine versus SSRIs in all patients and in the subgroup with more severe patients (final % responders on HAM-D-17).

SSRIs they were 50.19% (fluoxetine), 51.28% (sertraline), 40.98% (escitalopram), and 58.13% (escitalopram) in the FAS.

Clinical Global Impression of Improvement (CGI-I)

The CGI-I score at 24 weeks was significantly lower in patients treated with agomelatine than in patients treated with SSRIs. The overall estimate of the difference was 0.15 ± 0.07 points (P = 0.020) in the FAS and 0.17 ± 0.07 points (P = 0.020) in the subgroup of patients with severe depression.

The overall estimate of the difference in CGI-I response rates at the end of the 24 weeks was 3.82% (2.26) (P = 0.091) in the FAS and 4.41% (2.51) (P = 0.08) in the subgroup of patients with severe depression).

The overall estimate of the difference in CGI-I remission rates at the end of the 24 weeks was 2.09% (2.70) (P = 0.439) in the FAS and 1.60% (2.98) (P = 0.590) in the subgroup of patients with severe depression.

Completion rates

In the FAS, the percentage of patients who completed the 6-month treatment was 70.2% for patients treated with agomelatine versus 66.4% for patients treated with SSRIs [difference = 3.86 (2.60); P = 0.138] (Figure 4).

Tolerability and safety

The percentage of patients reporting at least one treatment emergent adverse event was not different in

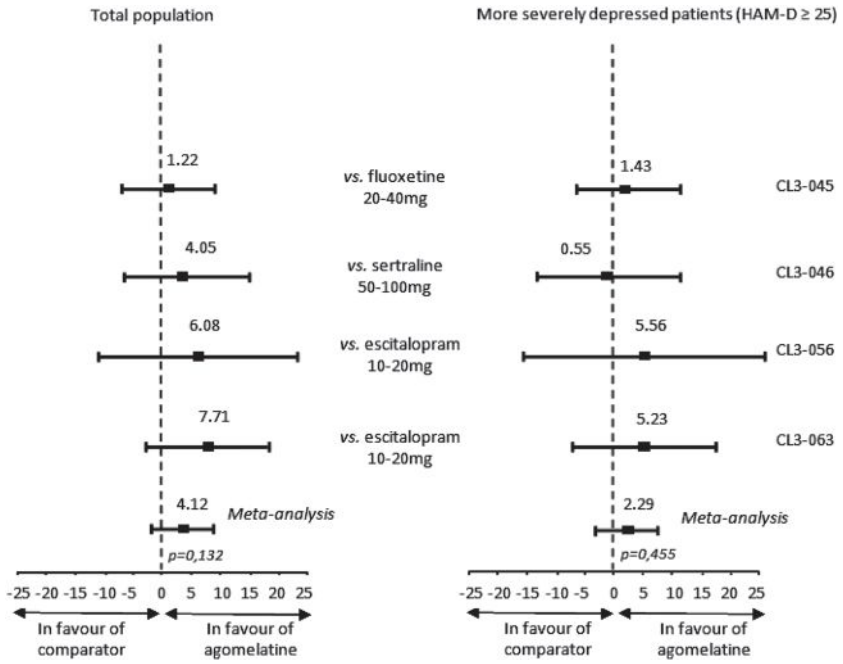

Figure 3. Long-term efficacy of agomelatine versus SSRIs in all patients and in the subgroup with more severe patients (final % remitters on HAM-D-17).

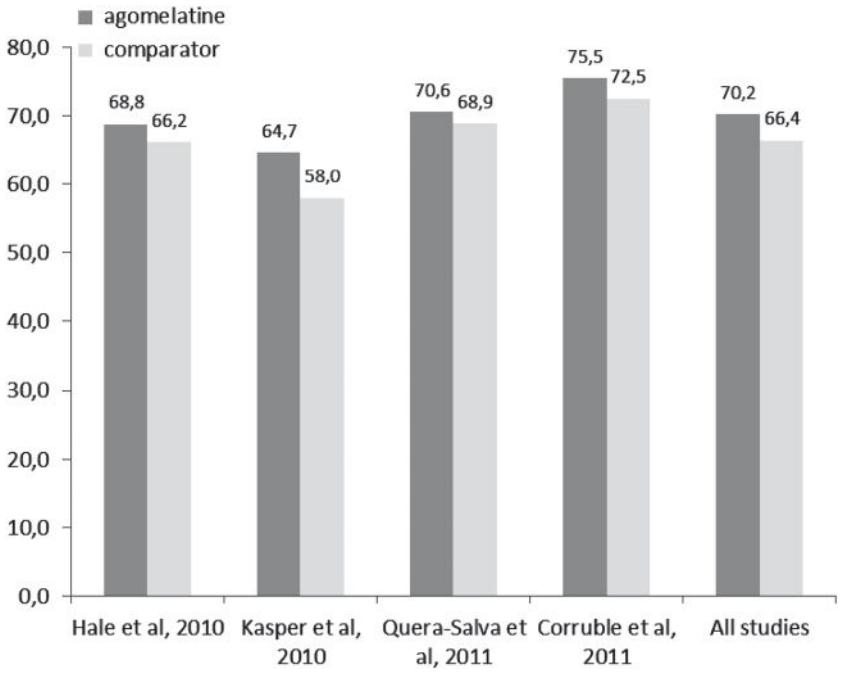

Figure 4. Percentage of patients who completed the 6-month trial with agomelatine or SSRIs.

patients treated with agomelatine than in patients treated with SSRIs (65.9% versus 67.4%). Psychiatric emergent adverse events were more frequently reported by patients treated with SSRIs than in patients treated with agomelatine (13.1% versus 7.6%; P = 0.001). The percentage of patients with at least one emergent adverse event leading to treatment discontinuation was 9.4% for patients treated with SSRIs versus 6.6% for patients treated with agomelatine (P = 0.065).

The percentage of patients spontaneously reporting treatment emergent sexual disorders was borderline significantly lower in patients treated with agomelatine

than in patients treated with SSRIs (2.9% versus 1.3%; P = 0.050). In male patients, treatment emergent sexual disorders were 3.6% with agomelatine and 8.7% with SSRIs (P = 0.076); in female patients, percentages were 0.4% and 0.7%, respectively (P = 0.685). The percentage of patients with a clinically significant (≥7%) weight increase was not different in patients treated with agomelatine and in patients treated with SSRIs (7.5% versus 8.7%, ie, 5.7% for fluoxetine, 9.6% for escitalopram, and 12.5% for sertraline). A change to an upper body mass index (BMI) class was noted in 8% of patients treated with agomelatine and in 7.7% of patients treated with SSRIs (6.4% for escitalopram, 7.6% for fluoxetine, and 10.3% for sertraline).

Significant emergent transaminase increases (>3 times the upper limit of normality) were found in 0.34% of patients treated with SSRIs (N = 2), 1.79% of patients treated with agomelatine 25 mg (N = 8), and in 2.61% in patients treated with agomelatine 50 mg (N = 4). The percentage of suicidal and self-injury behavior was not significantly different in patients taking agomelatine compared to patients taking SSRIs (0.8% versus 0.3%).

Discussion

The present meta-analysis shows that agomelatine has, compared with SSRIs, a statistically significant superiority for the HAM-D score, for the HAM-D response rate, and for the CGI-I score and a numerical but not statistically significant advantage for HAM-D remission rate, for CGI-I response rate, and for CGI-I remission rate. The magnitude of superiority is comparable in the total FAS and in the subgroup of patients with severe depression (baseline HAM-D ≥25), confirming the previously published efficacy of agomelatine through the full range of depression severity. A meta-analysis of 3 acute-phase treatment studies comparing agomelatine and placebo showed an increasing superiority over placebo with increasing baseline severity: a difference in final HAM-D of 2.06 for patients with a baseline HAM-D of 22–25, 3.31 for patients with a baseline HAM-D of 26–27, 3.46 for patients with a baseline HAM-D of 28–30, and 4.45 for patients with a baseline HAM-D of >30.[17]

However, although it is known that the outcome is better in head-to-head trials (where all patients get active treatment) compared to placebo-controlled trials, the HAM-D remission rates at 6 months in the present meta-analysis are only about 50%, again confirming the suboptimal results obtained with current depression treatment strategies.[18] A recently published open-label study in patients with major depressive disorder showed 6-month remission rates (LOCF) of only 32–35.5% depending on which antidepressant was used.[11]

The relevance of these differences in favor of agomelatine (a 5.09% superior HAM-D response rate) can be better understood when compared to differences found between other antidepressants or antidepressant groups. Combined serotonergic-noradrenergic antidepressants as well as escitalopram have been suggested to show "superior" efficacy compared to (other) SSRIs, at least in short term trials,[10,19] and the magnitude of the superiority was in the same range as reported here in the present meta-analysis. Indeed, a meta-analysis showed that 8-week response rates were 63.6% for combined serotonergic-noradrenergic antidepressants versus 59.3% for SSRIs (difference of 4.3%; P = 0.003).[10] Another meta-analysis showed that 8-week response rates were 62.1% for escitalopram versus 58.3% for the other SSRIs (difference of 3.8%; P = 0.0089).[19]

These findings again open the discussion on the difference between "statistically significant" superiority and "clinically meaningful" superiority (and "health economical" superiority). In trials comparing antidepressants with placebo, an NNT (numbers needed to treat) ≤10 is often suggested as clinically meaningful, while in trials comparing 2 active treatments, no such cut-off has been defined. So it is open to discussion how clinically meaningful the presently found differences are. A cautious statement could be that agomelatine is, from a clinical point of view, at least as efficacious as the 3 SSRIs in this meta-analysis, even if two studies included escitalopram, which is known to have some degree of superiority compared to other SSRIs.[19] The same reasoning can be applied on the difference in final HAM-D score (1.08 points), as the National Institute for Clinical Excellence guidelines consider a difference between an antidepressant and placebo of 3 points as "clinically meaningfull." The chance of getting an active antidepressant (depending on the number of treatment arms, and of a placebo arm or not) is known to significantly influence outcome, and in the present meta-analysis, all patients were treated with active medication, which makes it more difficult to find differences.[18]

However, what is a clinically meaningful difference cannot only be based on outcomes in randomized clinical trials alone, since only about 10% of daily practice patients can be included in RCTs due to inclusion and exclusion criteria, and hence results from RCTs cannot automatically be extrapolated to routine patients.[20,21]

The percentage of patients who completed the 6-month treatment in these 4 studies was numerically but not statistically significant higher for agomelatine than for the SSRIs. But again, although included in a clinical trial, only 2 patients of 3 continued their treatment up to 24 weeks, which is better than in a naturalistic setting, but below what guidelines

recommend. The low percentages of patients with at least one emergent adverse event leading to treatment discontinuation confirm the good tolerability of the antidepressants used in these 4 trials. The literature on which adverse events bother patients most is limited, but one study found that sexual side effects were reported to be the most bothersome side effects (47%) followed by insomnia (36.5%) and weight changes (35%).[22] The prevalence of treatment emergent sexual side effects differs depending on what methodology is used to assess these (spontaneous self-report versus questionnaires), and the present meta-analysis shows that statistically significantly fewer patients self-reported sexual side effects with agomelatine than with the SSRIs. This is in line with data from acute phase trials and with data in healthy volunteers where drug-induced sexual side effects were more frequent with venlafaxine and with paroxetine than with agomelatine.[23,24] The present meta-analysis also shows no significant differences in effect on body weight between agomelatine and the investigated SSRIs. Regarding safety issues, the percentage of dose-dependent treatment emergent transaminase increases are comparable with the figures reported in the acute phase trials. No statistically significant difference in suicidal or self-injury behaviors were noted in this meta-analysis, and the figures suggest that long-term treatment again does not represent an additional risk.

Conclusion

The present meta-analysis of 4 24-week, head-to-head trials comparing agomelatine with fluoxetine, sertraline, and escitalopram shows that, from a clinical point of view, agomelatine is at least as efficacious as the investigated SSRIs, with a trend to fewer discontinuations due to adverse events.

Disclosure

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CNS SPECTRUMS - Instructions for Contributors

Aims and scope

CNS Spectrums aims to be the premier journal covering all aspects of clinical neurosciences, neurotherapeutics and neurospsychopharmacology. From 2012 the journal will primarily focus on the publication of authoritative, cross-disciplinary review and opinion material publishing advances and controversial issues with pertinence to the clinician. In particular we aim to publish reviews and articles in translational neuroscience, biological psychiatry and neuropsychopharmacology that explain clinically relevant neuroscience discoveries in a way that makes these findings accessible and understandable to clinicians and clinical investigators. We will emphasize new therapeutics of all types in clinical neurosciences, mental health, psychiatry, and neurology, especially first-in-man studies and proof-of-concept studies. Our focus will be not just drugs, but novel psychotherapies and neurostimulation therapeutics as well. *CNS Spectrums* will in addition, continue to publish original research and commentaries that focus on emergent areas of research. Subject coverage shall span the full spectrum of neuropsychiatry focusing on translational issues and those crossing traditional boundaries between neurology and psychiatry.

Manuscript preparation

Article type descriptions

We will consider and encourage the following types of articles.

Original Research articles:

Articles in this category should present methodologically sound, new original study data that is in the following format: objective, methods, results, discussion, and conclusion. Suitable topics include mood disorders, schizophrenia and related disorders, personality disorders, substance-use disorders, anxiety disorders, neuroscience, psychosocial aspects of psychiatry, child psychiatry, geriatric psychiatry, and other topics of interest to clinicians in psychiatry, psychology, mental health disciplines, neurology and/or to clinical investigators in the neurosciences.

- 6,000 words; Up to 100 references
- 5–10 key words

Review articles:

Review articles should be concise, accessible, accurate and precise reviews of recent research and emergent areas. May include speculation and debate, but this should be clearly indicated. Focus on published authoritative and recent data from past 2–3 years. The introduction should be aimed at non-specialists and indicate the timeliness and rationale for the article. Inclusion of didactic and explanatory illustrations is strongly encouraged.

- 2,500–3,000 words; Up to 60 references
- Optional clinical implications summary
- 5–10 key words

Opinions:

An opinion article should be a personal viewpoint on a topical research topic, aimed to stimulate debate and new research. It should address a current topic of high interest, which has substantial evidence but has not yet been established. The opinion may be purposefully controversial, reinterpret the status quo, or speculate on future directions for research. It may also opine about socio-economic and policy issues relating to drug discovery, research and clinical intervention. Criticism of published material should be constructive and aim to lead the field in new directions.

- 2,000–3,000 words; Up to 30–60 references
- Optional clinical implications summary
- 5–10 key words

Commentaries:

A commentary will generally address a specific article or articles, either in the current issue or in a previously published issue of the journal. The commentary would be written either by the Editor-in-Chief, a member of the editorial board, or a reviewer or expert selected by the Editor-in-Chief or editorial board – often one of the reviewers for the manuscript that is the focus of the commentary. The manuscript would address how that article fits into that topic, and it would also address how the article advances the topic or changes a point of view or paradigm. Overall, a commentary is a commissioned manuscript that is written in reaction to previously published articles; usually encourages a certain level of debate.

- 1,500 words; Up to 6 references
- Optional clinical implications summary
- 5–10 key words

The following article types are for information only and unsolicited submissions shall not be considered.

Brainstorms:

Brainstorms are editorials or comments on a topic in the field, not directed towards content in the current issue, which provide a short background and overview of a current topic in the field or ongoing controversy or evolving point of view in the field and often provide illustrations of the topic as well in order to inform readers and set a context for them for the editorial opinion and commentary also included on that topic. Brainstorms, which are written by the Editor-in-Chief, have been an ongoing feature of the editor in chief in other journals for the past 15 years and will now continue exclusively in *CNS Spectrums*.

- 1,500 words; Up to 6 references
- 5–10 key words

Editorials:

Editorials, when submitted by an invited contributor, shall not be a simple listing of contents within the issue, but may for instance be used by the Guest Editor of a special issue or thematic section to introduce the subject being brought into focus. On occasion a luminary in the field might be approached to provide a guest editorial. Generally discursive in nature, an editorial will most likely form a short opinion piece or reflection upon the field but not constitute a full article.

- 1,500 words; Up to 10 references
- 5–10 key words

Abstract preparation

(format required for each article type):

- ***Reviews and Opinions*** The abstract should be unstructured (one paragraph, not divided into different sections) and no more than 250 words long.
- ***Original Research articles*** The abstract should be structured, i.e. divided into the following sections - Objective, Methods, Results, Conclusion, and no more than 250 words long.
- ***Brainstorms and Commentaries*** The abstract will be a very short summary, no more than 50 words long.
- ***Editorials*** shall not require an abstract, if one is included it will be a very short summary.

Clinical implications

Where appropriate, authors of reviews, opinions and commentaries may elect to also include a number of clinical implication points to be presented in addition to the abstract and conclusion. These will be most appropriate for articles that discuss material from preclinical studies and will be used to explain the findings and comment on their possible clinical applications.

Authors may include 3 to 5 points that are constructed as full sentences. They should be clear, unambiguous and aid the comprehension of the material being discussed.

Clinical implications will be assessed as part of the peer review process and authors may be asked to alter and update the points, or to remove them if they are not felt to add to the article.

Prior to submission

Although it is not required, for some review content, special series or special issues, prior to preparing a full-length manuscript, you may wish to consider sending a synopsis or abstract of your proposed submission for consideration by the Editor-in-Chief, Stephen Stahl. Please send to Lisa Arrington, Content Editor, *CNS Spectrums* (larrington@cambridge.org), so that we can first determine whether your submission is appropriate for consideration.

Formatting your article

The article type should be included in the upper right hand corner (original research, review article, opinion, etc.). Pages should be numbered consecutively in the upper right hand corner, beginning with the title page.

Original Research articles should be separated into the following sections: Title page, acknowledgements, abstract, introduction, Methods, Results, Discussion, Conclusion, References, Tables and/or Figures. Abstracts should be divided into specific sections as well (*please refer to the Article Type Description Grid for further details*).

Review articles should be arranged in the following order: Title page, acknowledgements, abstract (unstructured), introduction, body, conclusion, references, tables and figures. (*please refer to the Article Type Description Grid for further details*).

Co-authors' professional titles, departments, affiliations, and middle initials

The co-authors' names must be listed along with each person's professional title (Professor, Chairperson, Student, etc.), department (Department of Psychiatry, etc.), and professional affiliation (Johns Hopkins, Massachusetts General Hospital, Pfizer, etc.). If applicable, please also include each co-author's middle initial(s).

Figures/Tables:

- Original research article: Minimum 2 tables and/or figures
- Review article: Minimum 2 tables and/or figures; Maximum 6 tables and/or figures
- Opinions: Minimum 2 tables and/or figures; Maximum 6 tables and/or figures
- Commentaries: 1 table or 1 figure
- Editorial: 1 table or 1 figure

Please refer to the Article Type Description Grid for further details.

To ensure that your figures are reproduced to the highest possible standards and your article is published quickly and efficiently, please ensure that your figures are saved at final publication size and are in our recommended file formats (please see the latest issue of the journal for column widths).

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Funding

Please list sources of financial support (including grant numbers) for all authors.

Multiple grant numbers should be separated by a comma and a space. Where research was funded by more than one agency, the different agencies should be separated by a semi-colon, with 'and' before the final funder. Grants held by different authors should be identified as belonging to individual authors by the authors' initials. For example, 'This work was supported by the Wellcome Trust (A.B., grant numbers XXXX, YYYY), (C.D., grant number ZZZZ); the Natural Environment Research Council (E.F., grant number FFFF); and the National Institutes of Health (A.B., grant number GGGG), (E.F., grant number HHHH).'

References

Please use American Medical Association (AMA) style. References should be superscripted in text, then numbered, and comprehensive in list. Please number these references in the order that they appear in the text. These superscript numbers in the text should match the numbers and order of the references in the reference list (you should not list the references by alphabetical order). Abbreviations of journals' names should conform to the style used in *Index Medicus*; journals that are not indexed there should not be abbreviated. When following this format, please do not list any reference in your reference list more than once.

See the following examples:

- Journals:

  Goodkin K, Antoni MH, Helder L, et al. Psychoneuroimmunological aspects of disease progression among women and human papillomavirus-associated cervical dysplasia and human immunodeficiency virus type 1 co-infection. *Int J Psychiatry Med*. 1993;23(2):119–148.

- Books:

  Raine A. The Psychopathology of Crime: Criminal Behavior as a Clinical Disorder. San Diego, Calif: Academic Press; 1993.

- Parts of Books:

  Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FK, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. Baltimore, MD: Raven Press Ltd; 1995:1081–1097.

- Unpublished Materials:

  Eisenberg J. Market forces and physician workforce reform: why they may not work. Paper presented at: Annual Meeting of the Association of American Medical Colleges; October 28, 1995; Washington, DC.

  Jones JL, Hanson DL, Ward JW, et al. Incidence and trends in AIDS-related opportunistic illnesses in injecting drug users and men who have sex with men. In: Program and abstracts of the XI International Conference on AIDS; July 7–12, 1996; Vancouver, British Columbia. Abstract We.C.3418.

  Klassen TP, Watters LK, Feldman ME, et al. The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. Pediatrics. In press.

Manuscript submission

Submission:

Please submit your manuscript directly to *CNS Spectrums* via the CNS ScholarOne Manuscripts website: mc.manuscriptcentral.com/cnsspectr.

Set up or login to your account, enter your Author Center, follow the instructions carefully, and upload your manuscript for submission.

A generic Author Quick Start Guide is available to download from:
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Once you submit your manuscript you will receive an automated e-mail confirmation stating that your manuscript was submitted successfully. In addition, a manuscript reference number will be generated for your submission automatically. If we decide to consider your manuscript for publication, our Editor-in-Chief will assign it to a Field Editor and peer reviewers. The unique reference number of the manuscript should be quoted in all correspondence with the CNS Spectrums' Office and Publisher.

Peer review and revision process

Peer reviewer suggestions:

Authors must provide at minimum of three (3) names of qualified potential reviewers with the necessary contact information (affiliation and e-mail address). Reviewers should be specialists in the topic of the submitted paper, who have no conflict of interest and who are not affiliated with the company, organization, or institution that employ any of the co-authors of the manuscript. We may contact one or more of your suggested reviewers once we receive your manuscript, but we reserve the right to not do so. Peer review is anonymous.

Revision process:

The Field Editor and/or Editor-in-Chief will check the reviewers' overall assessment of the article. Peer review comments are then forwarded to the corresponding author for revisions. Authors are expected to incorporate all revisions to the best of their ability, unless otherwise noted. In addition, the authors' list of incorporated changes must accompany their revised manuscript. Authors are expected to submit revised manuscripts by the designated due date(s).

If there are any questions about the reviewers' comments and/or suggested revisions, please contact the Field Editor and/or Content Editor directly, who will follow-up with the reviewer(s) for further clarification.

Failure to meet deadlines during the revision process

It is very important that authors meet all deadlines for submitted material (manuscripts, revisions, etc.). If you have problems meeting your deadlines, please call the Field Editors of *CNS Spectrums* or contact Lisa Arrington, Content Editor, at larrington@cambridge.org and explain your situation. You may be granted an extension. However, please note that late draft submissions are problematic. If delays start to significantly jeopardize our publication schedule, your article will be cut.

Post-acceptance/Production workflow

Upon final acceptance of a manuscript for publication, it is passed on to our production department, who will send it out for copyediting. The copyeditor will be in contact with the corresponding author directly regarding any queries about the article. The Corresponding author will need to respond to the copyeditor in a timely manner (usually within 48 hours), to ensure the prompt and efficient processing of the article. Typeset proofs shall be issued to the corresponding author as a final check – no substantive change shall be introduced at this stage.

Once the typeset version is posted on the Cambridge Journals Online web site, please note that it cannot be changed, as it will constitute the version of record (VoR).

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All articles will be prepared for publication immediately upon their acceptance and published online in full before being allocated to an issue. Our intention is to allocate articles to the next available issue in order of date of acceptance. From time to time we are forced to allocate the publication accepted manuscripts to later issues in order to accommodate thematic content.

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Papers with multiple authors are reviewed with the assumption that all authors have contributed materially to the research reported, have approved the submitted manuscript, and concur with its submission to *CNS Spectrums*. A Copyright Transfer Agreement, with certain specified rights reserved by the author, must be signed and returned to the Publisher by each co-author listed at the time of submission. This is necessary for the wide distribution of research findings, and the protection of both author and Cambridge University Press under copyright law.

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Originality and Copyright

To be considered for publication in *CNS Spectrums*, a manuscript cannot have been published previously, nor can it be under review for publication elsewhere. (Previously published figures may be sparingly used in Reviews, with appropriate permission.)

If you have an article currently under review pending a decision, you are welcome to keep it submitted to the journal or withdraw it at anytime. **However, if you decide to submit your article to a different publication, you must officially withdraw it from *CNS Spectrums* before submitting it elsewhere**. You can withdraw your paper through the Author Center on the CNS ScholarOne Manuscripts site. Alternatively, you may send an e-mail request specifying that you are asking to withdraw your manuscript and you must include the manuscript title and the names of your co-authors (if applicable), and the unique article identifier issued upon submission.

The posting of a brief summary of clinical trial outcomes on a pharmaceutical website (such as the PhRMA-sponsored database <www.clinicalstudyresults.org>) will not necessarily count as prior publication nor impede full consideration of a manuscript: *CNS Spectrums* will look at this on a case-by-case basis to determine the extent of overlap between the trial data posted and the manuscript as submitted, and will decide whether the manuscript contains sufficiently new perspectives or sufficient additional data for it to count as original. Authors should declare when submitting manuscripts that such data have already been posted and *CNS Spectrums* will review this sympathetically.

Clinical Trials

As a condition of consideration for publication, registration of clinical trials in a public trials registry is required. A clinical trial is defined by the International Committee of Medical Journal Editors (in accordance with the definition of the World Health Organisation) as any research project that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Trials must be registered before the start of patient enrollment. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum a unique trial number, trial registration date, secondary identification information if assigned by sponsors or others, funding source(s), primary and secondary sponsor(s), responsible contact person, research contact person, official scientific title of the study, research ethics review, the medical condition being studied, intervention(s), key inclusion and exclusion criteria, study type, anticipated trial start date, target sample size, recruitment status, primary outcome, and key secondary outcomes. Registration information must be provided at the time of submission. Trial registry name, registration identification number, and the URL for the registry should be included at the end of the abstract.

Manuscripts reporting the results of randomized controlled trials should include a "CONSORT" flow diagram as a figure in the manuscript to illustrate the progress of all patients in the study (See: Schulz KF, Altman D, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987–1991.)

Ethical considerations

Papers reporting experiments involving human subjects must contain the statement that the research was approved by an Internal Review Board, Helsinki Committee or similar body and that subjects gave informed consent. Papers describing animal experiments must indicate that the research was approved by a Review Committee or clearly state that the experiments were performed in accordance with accepted guidelines such as 'Guiding principles in the care and use of animals (DHEW Publications, NIH, 80-23). Papers that do not contain an Ethics Statement will not be reviewed.

Summary of article types and requirements

Article type	Length	Abstract	Figs/ Tables	Purpose/ features
Original research	• 6,000 words • Up to 100 references	• Structured • ≤ 250 words • No citations	• Minimum 2 tables and/or figures	Original Research: Reports the results of a formal study based on original research. • Structured abstract
Review article	• 3,000 words • Up to 60 references	• Unstructured • ≤ 250 words • No citations	• Minimum 2 tables and/or figures • Maximum 6 tables and/or figures	Review: Written as a literature review of an established topic, as suggested by its name. • Clinical implication points
Opinions	• 3,000 words • 30–60 references	• Unstructured • ≤ 150 words • No citations	• Minimum 2 tables and/or figures • Maximum 6 tables and/or figures	Opinion: Addresses a current topic of high interest, which has substantial evidence but has not yet been established. • Clinical implication points
Commentaries	• 1,500 words • Up to 6 references	• Unstructured • ≤ 100 words • No citations	• 1 table or 1 figure	Commentary: Commissioned manuscript that is written in reaction to previously published articles; usually encourages a certain level of debate. • Clinical implication points
Editorial	• 1,000 words	• Unstructured • 150 words	• 1 table or 1 figure	Editorial: Introduces a new idea or a particular theme, usually written by the editor-in-chief and occasionally submitted by a guest editor.

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