

Multifunctional Drugs: A Novel Concept for Psychopharmacology

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NEW TREND IN PSYCHOPHARMACOLOGY

Beginning this month and appearing periodically in future columns, "Trends in Psychopharmacology" will cover a new concept and hot topic in the field, namely, that of "multifunctional drugs." The concept is presented in overview here. Future installments will cover specific drugs in greater depth. Multifunctional drugs include those agents with more than one putative therapeutic mechanism of action.

WHAT IS A MULTIFUNCTIONAL PSYCHOTROPIC DRUG?

Multifunctional drugs are those agents with more than one therapeutic mechanism. Almost all drugs have more than one known pharmacologic action, especially at doses higher than those used therapeutically. However, many of these additional mechanisms are considered unwanted and the cause of side effects rather than therapeutic effects.

For example, the tricyclic antidepressants (TCAs) have many known pharmacologic actions, but their ability to block the norepi-

nephrine transporter (NET) and/or the serotonin transporter (SERT) are the properties most consistently attributed to mediating their antidepressant actions.¹ More recently, the ability of some of these agents to block serotonin (5-HT) receptor subtypes as well (particularly the 5-HT_{2A} and 5-HT_{2C} receptors) has been linked to antidepressant therapeutic actions.¹ However, the ability of TCAs to block muscarinic cholinergic receptors, α_1 adrenergic receptors, and histamine H₁ receptors at therapeutic doses, and sodium channels at overdose levels, are generally considered to be the cause of side effects.¹ When an undesired pharmacologic action occurs at therapeutic doses, this is not a multifunctional drug, but a "dirty drug." Two or more therapeutic actions are what make a drug multifunctional rather than dirty.

AREN'T ALL DRUGS MULTIFUNCTIONAL?

At some level, almost all psychotropic drugs have multiple pharmacologic actions, and, indeed, many of these actions are considered to be therapeutic. TCAs, according to the definitions given above, are thus both multifunctional and dirty. On the other hand, serotonin-norepinephrine reuptake inhibitors (SNRIs) are multifunctional but not dirty, since they retain the NET and SERT inhibitory properties of TCAs,

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Faculty Disclosures: Dr. Stahl has served as a consultant to Arena, Azur, Bionevia, BristolMyers Squibb, Eli Lilly, Endo, Forest, Jazz, Johnson & Johnson, Labopharm, Lundbeck, Marinus, Neuronetics, Novartis, Noven, PamLab, Pfizer, Pierre Fabre, Sanofi, Sepracor, Servier, Shire, SK Corporation, Solvay, Somaxon, Tetraxenex, and Vanda; he has served on speaker's bureaus for Pfizer and Wyeth; and has received grant support from Forest, Johnson & Johnson, Novartis, Organon, PamLab, Pfizer, Sepracor, Shire, Takeda, Vanda, and Wyeth.

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but not the anticholinergic, antiadrenergic, and antihistamine properties.¹

A list of various psychotropic agents that can be considered multifunctional is given in Table 1. This includes much of the current armamentarium of psychopharmacology. Drug nomenclature is moving toward naming an agent based upon all of its therapeutically linked pharmacologic properties, and not by its clinical action or actions. Thus, is a drug an antidepressant (old fashioned) or a serotonin selective reuptake inhibitor (SSRI) or an SNRI (multifunctional)? Some SSRIs have important secondary properties; so should they be called "not-so-selective serotonin reuptake inhibitors"?^{1,2} Or should SSRIs and SNRIs be called anxiolytics, since most of them are also approved for up to five different anxiety disorders?

Similarly, what is a mood stabilizer? An anti-convulsant? Some anticonvulsants? Lithium? Or the atypical antipsychotics?

In fact, what is an atypical antipsychotic when all of them treat nonpsychotic mania and some of them treat bipolar and unipolar depression as well?^{1,3}

TABLE 1.
Seeing Various Psychotropic Agents in Clinical Practice From a Multifunctional Perspective

<i>All TCAs</i>	<i>Trazodone</i>
Doxepin	<i>Mirtazapine</i>
Clomipramine	<i>Atypical Antipsychotics</i>
Others	Risperidone
<i>SNRIs</i>	Olanzapine
Venlafaxine	Quetiapine
Desvenlafaxine	Ziprasidone
Duloxetine	Clozapine
Milnacipran	Aripiprazole
<i>Some SSRIs</i>	<i>Benzodiazepines</i>
Sertraline	<i>Some "Z" Drugs</i>
Fluoxetine	Eszopiclone
Paroxetine	Zopiclone

Bupropion

TCAs=tricyclic antidepressants; SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors.

Stahl SM. *CNS Spectr.* Vol 14, No 2. 2009.

The dilemma in drug classification is thus clear and explains the movement toward multifunctional pharmacologic drug categorization. To accentuate the timeliness of this paradigm shift in drug classifications, an entire issue of a recent journal is dedicated to various multifunctional drugs in neurology and psychiatry.⁴

TABLE 2.
Future Multifunctional Psychotropic Agents in the Pipeline

<i>Agents</i>	<i>Pharmacologic Actions</i>	<i>Proposed Clinical Actions</i>
Triple reuptake inhibitors	Serotonin, norepinephrine, and dopamine transport inhibitors	Antidepressant plus
Agomelatine	M ₁ and M ₂ agonist, 5-HT _{2C} antagonist	Antidepressant, hypnotic, anxiolytic plus
Asenapine	Atypical antipsychotic	Antipsychotic, antimanic, antidepressant plus
Iloperidone	Atypical antipsychotic	Antipsychotic, antimanic, antidepressant plus
Lurasidone	Atypical antipsychotic	Antipsychotic antimanic antidepressant possible pro-cognitive agent plus
LuAA21004	Serotonin reuptake inhibitor, 5-HT _{1A} partial agonist, 5-HT ₃ antagonist	Antidepressant, anxiolytic plus
LuAA24530	Triple reuptake inhibitor plus	Antidepressant, anxiolytic plus
Cariprazine	D ₃ preferring and D ₂ partial agonist	Antipsychotic, antimanic, antidepressant plus
Tasimelteon	Balanced M ₁ and M ₂ agonist	Jet lag, circadian rhythm regulator, hypnotic plus
Flibanserin	5-HT _{2A} antagonist, 5-HT _{1A} partial agonist, 5-HT _{2C} antagonist	Hypoactive sexual desire disorder plus

M=melatonin; 5-HT=serotonin; D=dopamine.

Stahl SM. *CNS Spectr.* Vol 14, No 2. 2009.

The point is that modern psychopharmacology is experiencing a paradigm shift in drug classification, moving toward an emphasis on every relevant pharmacologic mechanism that is linked to a therapeutic action, not to a single clinical action.

DOSE-DEPENDENT MULTIFUNCTIONALITY: DEPENDS UPON DOSE

One nuance of the multifunctional concept is that a molecule may have different functions at different doses, depending upon the potency of its multiple pharmacologic actions. In fact, this was recently presented in another "Trends In Psychopharmacology" column⁵ where the TCA doxepin was shown to be a selective H₁ antagonist when given at a fraction of its antidepressant dose. At low doses, doxepin is so selective for H₁ receptors that it makes an excellent binding ligand for in vitro studies and positron emission tomography scans.⁵ Only upon raising the dose 10–100 fold does it become an antidepressant, as the higher doses recruit additional pharmacologic properties.⁵

Another example of a dose dependent multifunctional psychotropic drug is trazodone. At low doses, it is a hypnotic but not an antidepressant.¹ Low doses act at 5-HT_{2A} receptors, H₁ receptors and α_1 receptors, and cause sedative hypnotic clinical actions. If the dose is raised 3–5 fold to recruit the blockade of SERT, trazodone becomes an antidepressant as efficacious as SSRIs or TCAs.¹

The concept of multifunctionality can be exploited to find expanded clinical uses for a psychotropic drug. One of the best examples of this may be quetiapine. Originally used as an antipsychotic and antimanic agent when given at high doses that block a substantial number of dopamine D₂ and 5-HT_{2A} receptors, like all known atypical antipsychotics,¹ quetiapine has been used as a hypnotic at very low doses. Perhaps like doxepin,⁵ this low-dose hypnotic use is linked to quetiapine's potent H₁ antagonist actions. Furthermore, intermediate doses of quetiapine show robust actions in both bipolar depression and unipolar depression, potentially linked to the pharmacologic properties of an active metabolite that blocks NET as well as 5-HT_{2C} receptors.¹

CONCLUSION

Whether by design or by serendipity, almost all new psychotropics in development exhibit multifunctional properties. Several examples are given in Table 2. As these agents move forward in clinical development, selected examples will become the focus of future installments of "Trends in Psychopharmacology". **CNS**

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