Dual- and Triple-Acting Agents for Treating Core and Co-morbid Symptoms of Major Depression: Novel Concepts, New Drugs

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Summary: The past decade of efforts to find improved treatment for major depression has been dominated by genome-driven programs of rational drug discovery directed toward highly selective ligands for nonmonoaminergic agents. Selective drugs may prove beneficial for specific symptoms, for certain patient subpopulations, or both. However, network analyses of the brain and its dysfunction suggest that agents with multiple and complementary modes of action are more likely to show broad-based efficacy against core and comorbid symptoms of depression. Strategies for improved multitarget exploitation of monoaminergic mechanisms include triple inhibitors of dopamine, serotonin (5-HT) and noradrenaline reuptake, and drugs interfering with feedback actions of monoamines at inhibitory 5-HT_{1A}, 5-HT_{1B} and possibly 5-HT_{5A} and 5-HT_7 receptors. Specific subsets of postsynaptic 5-HT receptors mediating antidepressant actions are under study (e.g., 5-HT_4 and 5-HT_6). Association of a clinically characterized antidepressant mechanism with a nonmonoaminergic component of activity is an attractive strategy. For example, agomelatine (a melatonin agonist/5-HT_{2C} antagonist) has clinically proven activity in major depression. Dual neurokinin$_1$ antagonists/5-HT reuptake inhibitors (SRIs) and melanocortin$_4$ antagonists/SRIs should display advantages over their selective counterparts, and histamine H_3 antagonists/SRIs, $GABA_B$ antagonists/SRIs, glutamatergic/SRIs, and cholinergic agents/SRIs may counter the compromised cognitive function of depression. Finally, drugs that suppress 5-HT reuptake and blunt hypothalamo–pituitary–adrenocorticotrophic axis overdrive, or that act at intracellular proteins such as GSK-3β, may abrogate the negative effects of chronic stress on mood and neuronal integrity. This review discusses the discovery and development of dual- and triple-acting antidepressants, focusing on novel concepts and new drugs disclosed over the last 2 to 3 years. **Key Words:** Antidepressant, multitarget, network, stress, HPA axis, CRF.

FROM HIGHLY SELECTIVE AGENTS TO MULTITARGET ANTIDEPRESSANTS

Major depression is a common, heterogeneous, and often incapacitating disorder triggered by a complex pattern of genetic, epigenetic, developmental, and environmental factors.[1] Although commonly used antidepressants, such as the selective serotonin (5-HT) reuptake inhibitor (SSRI) fluoxetine, are often effective, full efficacy is only apparent after several weeks; and many patients only partially respond, and some remain refractory. Accordingly, considerable efforts are invested in the search for better drugs (and other, nonpharmacotherapeutic approaches) for more effective treatment of depression.[2–8] There is a need for improved control not just of affective deficits, but also of other symptoms, such as insomnia, circadian desynchronization, sexual dysfunction, cognitive impairment, and pain. Moreover, depression shows high comorbidity with other serious CNS disorders (Table 1).[3,7]

All currently available antidepressants harness monoaminergic mechanisms. The past decade has witnessed a genome-driven focus on the rational discovery of highly selective drugs acting at innovative, nonmonoaminergic targets (FIG. 1).[3–9] Along with genetically modified mice as animal models, such agents are vital in the experimental and therapeutic exploration of novel drug targets and hypotheses. In addition, selective antidepressants may prove helpful against particular symptoms and in discrete subpopulations of patients who have specific pathologies.[1,3] Nonetheless, agents that interact with several complementary targets or with distributed cerebral networks (or with both) offer greater hope for the broad-

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Table 1. *Symptoms and CNS Disorders Frequently Comorbid with Major Depression*

	Symptom								
Disorder	Depressed Mood	Anxiety	Cognitive Perturbation*	Decreased Sleep Quality	Circadian Disruption	Sexual Dysfunction	Psychosis or Mania	Pain	Motor Retardation or Excitation
Major depression	+++	++	++	++	++	+	+	+	++
Anxiety disorders	++	+++	++	++	+	+	−	+	++
Bipolar disorder	++	+	++	++	++	+	+++[†]	−	+
OCD	+	++[‡]	++	+	+	+	+	−	+
Schizophrenia	+	+	++	+	+	+	+++	+	++
Parkinson's	++	+	++	++	+	++	+	++	+++
Alzheimer's	+	+	+++	++	++	NR	++	−	++
Epilepsy	+	+	++	++	+	+	−	+	−
Stroke	++	+	+++	+	+	+	+	++	++
Chronic pain	++	++	+	++	+	++	+	+++	++

OCD = obsessive compulsive disorder; NR = not usually relevant; +++ = cardinal; ++ = prominent; + = well recognized; − = not characteristic.
*Cognitive perturbation is a complex construct, with patterns of disruption differing markedly among disorders.
[†]Mania.
[‡]Cause? Or consequence? Or both?

based and efficacious treatment of both cardinal and comorbid symptoms of depression.[3,7,10–16]

The present author has, elsewhere, comprehensively discussed conceptual bases underpinning multitarget antidepressants, and reviewed a broad range of mechanisms implicated in the pathogenesis and potentially improved control of affective disorders.[3] The present review outlines the principal advances of the last few years, focusing on the discovery and development of drugs that have dual and triple mechanisms of antidepressant activity.

THE SEARCH FOR DUAL- AND TRIPLE-ACTING ANTIDEPRESSANTS: RATIONALE

Numerous arguments support the contention that multitarget mechanisms may be more effective and better tolerated than their highly selective counterparts in the management of CNS disorders (see elsewhere in this issue). Several lines of evidence specifically substantiate interest in dual- and triple-acting antidepressants.

First, there is no single cause of major depression. Rather, a vast array of interacting genes, epigenetic influences, developmental events, and environmental influences collectively (and often synergistically) compromise mood and trigger affective disorders.[1] Despite contemporary notions of endophenotype (i.e., gene-related dysfunction specific to an individual), genetic screening, and individual medicine,[1,17] treatment strategies with a broad influence on corticolimbic circuits implicated in depression are more likely than highly selective agents to be effective in significant patient numbers.

Second, agents that have complementary components of action have a greater chance of controlling both the mood deficits of depression and other symptoms reflecting contrasting pathophysiological substrates, such as mnemonic deficits, desynchronization, and pain.[1,3]

Third, coadministration of various classes of adjunctive agent, from lithium to atypical antipsychotics to thyroxine, reinforces the efficacy of SSRIs.[3,18–22] This is clearly not equivalent to an increase in dose: improved efficacy reflects engagement of mechanisms complementary to 5-HT reuptake inhibition—not just more of the same, but something different on top.

Fourth, prototypical drugs for the treatment of other major psychiatric and neurological disorders act *via* a diversity of neuronal mechanisms distributed across many cerebral regions (Table 2). Similarly, pharmacological, somatic, and psychological approaches for relieving depression are unlikely to act *via* any common unitary mechanism.

Fifth, in line with this assertion, sleep deprivation (rapidly effective) and electroconvulsive therapy (active in many drug-refractory patients), as well as deep brain stimulation, transcranial magnetic stimulation, and vagal nerve stimulation (although data are less extensive), engage a broad array of molecular substrates[3,6,7,23] and, as suggested by imaging studies, extensive cerebral circuits (Table 3).[23–27] The same holds for psychological approaches such as cognitive-behavioral therapy, which likewise affect overarching cerebral networks rather than any single circumscribed brain region.[28–30] This is a far cry, then, from a highly selective drug targeting a single protein (Table 3). Ideally, one should identify the key

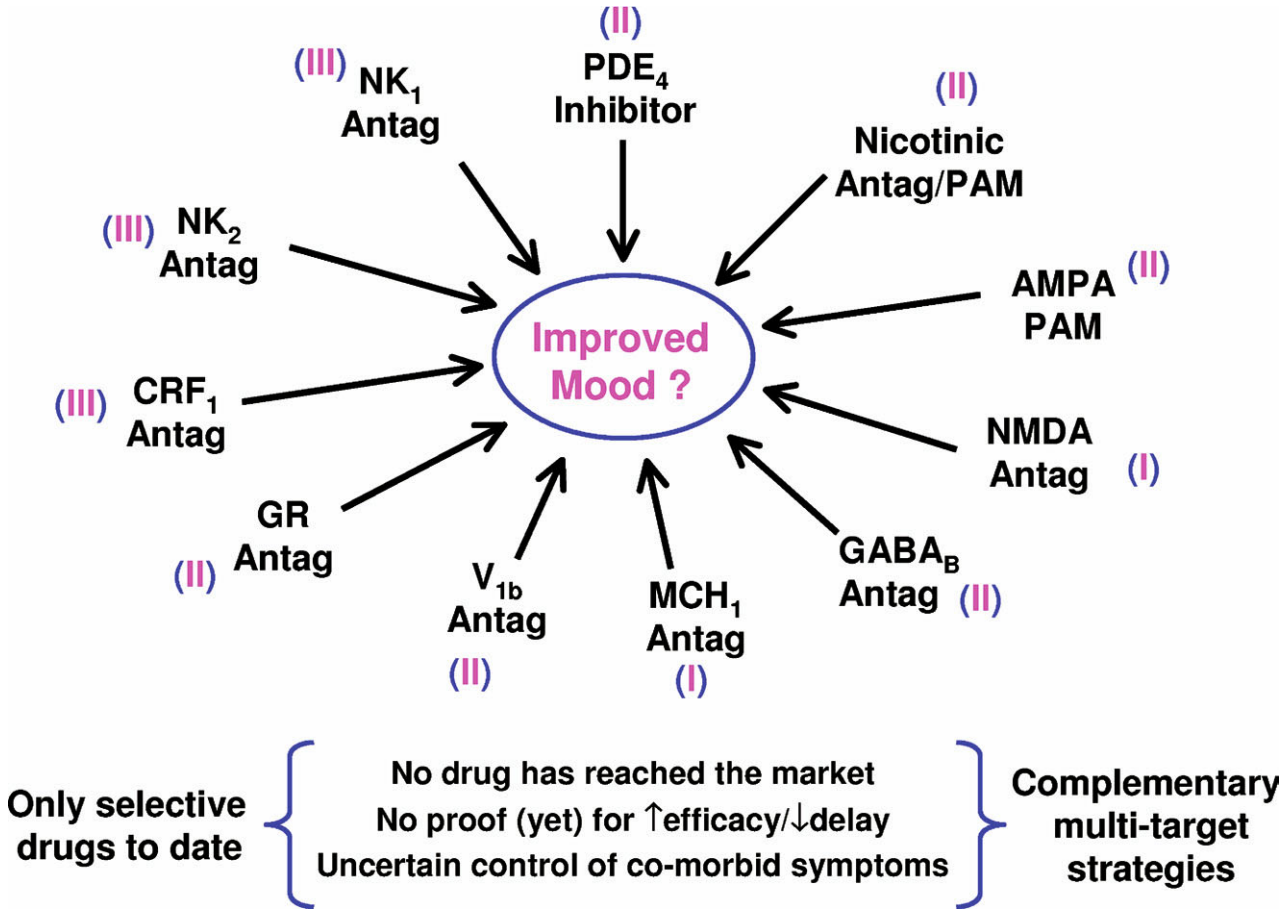

FIG. 1. Nonmonoaminergic mechanisms for treatment of major depression under clinical investigation with selective drugs. Numbers in Roman numerals refer to the highest phase of clinical development attained to date. Certain mechanisms are being evaluated for other indications, such as AMPA receptor facilitators, PDE-4 inhibitors, and nicotinic modulators for Alzheimer's disease. There is still no proof that selective drugs acting *via* such nonmonoaminergic mechanisms can robustly treat depression. Antag = antagonist; CRF = corticotrophin releasing factor; GR = glucocorticoid receptor; MCH = melanin concentrating hormone; NK = neurokinin; PAM = positive allosteric modulator; PDE = phosphodiesterase; V = vasopressin.

mechanisms of such treatments and transform them into more accessible multitarget agents—although this is unlikely to prove simple.

Sixth, suppression of the muscarinic and histamine H_1 antagonist properties of tricyclic drugs, and elimination of their actions at cardiac ion channels, has led to the far safer SSRIs.[3,7,31,32] Nonetheless, the belief that selective drugs are inherently better tolerated than equivalent multitarget agents is ill-founded. One familiar example is provided by selective cyclooxygenase-2 (COX_2) inhibitors, which present greater problems of cardiovascular security than drugs with balanced actions relative to COX_1.[33] Furthermore, dopamine D_2 antagonists with marked 5-$HT_{2A/2C}$ receptor antagonist properties have a lesser propensity to elicit an extrapyramidal syndrome.[34] By analogy, 5-HT reuptake inhibitors with equilibrated antagonist properties at 5-HT_{2C} sites should have tolerability superior to that of SSRIs, because certain of their undesirable actions, such as short-term anxiety, derive from stimulation of 5-HT_{2C} sites (discussed later in this article).

In the search for dual-acting, triple-acting, and higher orders of multitarget agents, essentially three classes of ligand are of interest, from both a conceptual and a clinical perspective. First are drugs with exclusively monoaminergic targets, but mechanistically distinct from (and superior to) SSRIs, tricyclics, and other currently available classes of agent due to either or both 1) deletion of sites provoking adverse effects, and 2) incorporation of new targets underlying beneficial actions (FIG. 2). Second are drugs acting at combinations of nonmonoaminergic targets—although none have as yet been developed. Third, and most promising, are agents with a clinically validated monoaminergic mechanism, such as suppression of 5-HT reuptake or blockade of 5-HT_{2C} receptors, plus a novel, nonmonoaminergic mechanism of action to refine the therapeutic profile (FIG. 3).

Table 2. *Multitarget and Network-Based Actions of Prototypical Drugs Used for Treating CNS Disorders*

Disorder	Class (Drug)	Principal Effects	Major Loci of Action	Adverse Effects
Major depression	Tricyclic (amitriptyline)	5-HT/NA reuptake inhibition; 5-$HT_{2A/2C}$ receptor blockade	FCX; septum; hippocampus	Poor autonomic/CV tolerability due to H_1/muscarinic blockade; cardiotoxicity (Na^+/Ca^{2+} channels)
Bipolar disorder	Ion (lithium)	↓ IP production; GSK-3β inhibition*; ↓ glutamate release	Cortex; hippocampus; amygdala; thalamus	Muscular weakness; toxicity; hyperdipsia
Generalized anxiety disorder	Benzodiazepine (clorazepate)	$GABA_A$ positive; modulator, ~17 subunits; > 100 subtypes	Hippocampus; amygdala; PAG; LC; DRN	Sedation; alcohol interaction; dependence; tolerance
Schizophrenia	Atypical (clozapine)	D_1–D_5; 5-$HT_{1A/2A/2C/6/7}$ and α_1/α_2-AR receptors; GABAergic and glutamate modulation	FCX; nucleus accumbens; hippocampus; thalamus	Poor autonomic/CV tolerability due to H_1/muscarinic blockade; agranulocytosis (structure-related); seizures
Alzheimer's disease	Acetylcholinesterase inhibitor (galantamine)	Nicotinic modulator; butyrylcholinesterase inhibitor; ↓ β-amyloid production	Cortex; hippocampus	Poor tolerability; (cholinergic adverse effects)
	Noncompetitive NMDA antagonist (memantine)	Rapid-kinetic NMDA channel blocker; 5-HT_3 antagonist; nicotinic modulator	Cortex; hippocampus	Overall mild; confusion; tiredness; hallucinations
Parkinson's disease	DA precursor (L-DOPA)	↑ DA recruits D_1–D_5 sites; serotonergic, glutamatergic, and other mechanisms	Striatum; substantia nigra; nucleus accumbens; subthalamic nucleus; FCX	Wearing-off; dyskinesia

Increases in levels of 5-HT, noradrenaline, DA, or acetylcholine will indirectly recruit multiple classes of serotonergic, adrenergic, dopaminergic, and nicotinic/muscarinic receptors, respectively. Autonomic and cardiovascular adverse effects mainly, but not only, reflect blockade of histaminergic (H_1) and muscarinic receptors.
CV = cardiovascular; DA = dopamine; DRN = dorsal raphe nucleus; FCX = frontal cortex; 5-HT = serotonin; IP = inositol phosphate; LC = locus coeruleus; PAG = periaqueductal gray area; ↑ (↓) = increased (decreased).
*Indirect and direct.

NOVEL DUAL- AND TRIPLE-ACTING MONOAMINERGIC ANTIDEPRESSANTS

Return to the future: the promise of novel monoaminergic strategies

Reflecting the crucial role of monoamines in the control of mood, cognition, motor behavior, and other functions disrupted in depression, monoaminergic drugs remain the cornerstone of treatment, nearly 50 years after the discovery of tricyclics.[3,7,35,36] The SSRIs and noradrenaline (NA) reuptake inhibitors (NARIs) are not more effective than tricyclic agents and, despite the (overall) more robust actions of mixed 5-HT/NA re-

Table 3. *Multiple Mechanisms Involved in Actions of Somatic Antidepressant Interventions*

	5-HT	NA	DA	Opioid	Galanin	BDNF
Tricyclic antidepressants	↑	↑	↑	↑	↑	↑
Sleep (REM) deprivation	↑	↑	↑	↑	↑	↑
Electroconvulsive therapy	↑	↑	↑*	↑	↑	↑
Vagal nerve stimulation	↑	↑	↑/−	?	?	↑
Transcranial magnetic stimulation	↑	↑/−	↑	↑	?	↑

Apart from endogenous opioid peptides and galanin, many other neuropeptides are variously affected by these treatments (e.g., substance P, neuropeptide Y, corticotrophin releasing factor, and vasopressin). Many corticolimbic structures are affected, as revealed by imaging studies discussed in the text. For more details, see Millan, 2006.[3]
BDNF = brain-derived neurotrophic factor (serum levels in patents); DA = dopamine; NA = noradrenaline; REM = rapid eye movement; ? = little concrete information is available.
*Increased transmission at postsynaptic level.

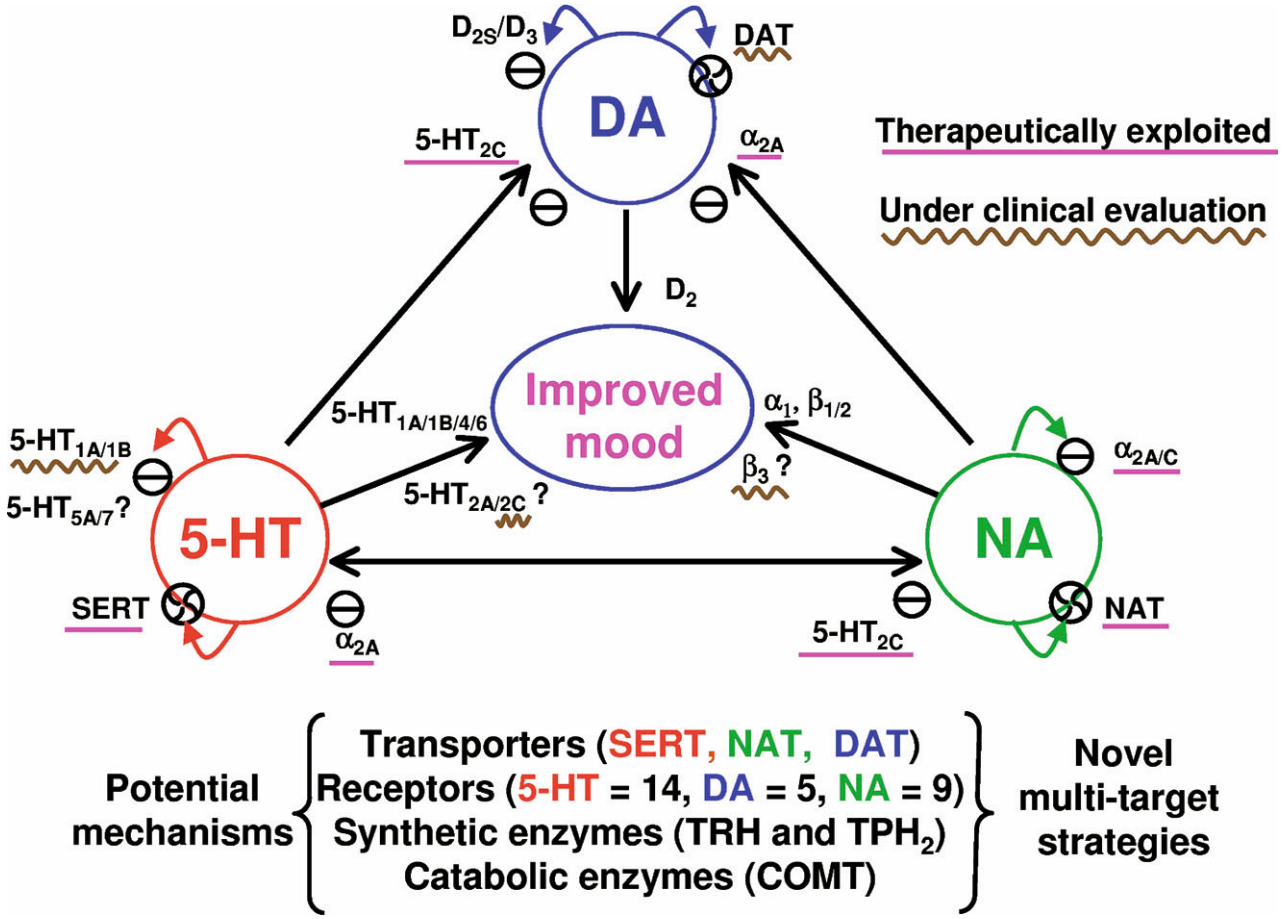

FIG. 2. Monoaminergic strategies for improving the management of depression: scope for further exploitation. Interacting monoaminergic pathways control mood, and their perturbation contributes to the induction of depression. Antidepressants in clinical use act principally by inhibiting monoamine oxidase (not shown), or by suppressing reuptake of either or both 5-HT and NA or by blocking 5-HT_{2C}/α_2-adrenergic receptors, or by both reuptake inhibition and receptor blocking mechanisms. Unexploited opportunities remain for acting at diverse monoaminergic receptors; TRH, which generates NA and DA; TPH_2, which yields 5-HT; COMT, which catabolizes DA; and DAT. COMT = catecholamine methyl transferase; DA = dopamine; DAT = dopamine transporter; 5-HT = serotonin; NA = noradrenaline; NAT = noradrenaline transporter; SERT = serotonin transporter; TRH = tyrosine hydroxylase; TPH = tryptophan hydroxylase.

uptake inhibitors (SNRIs) such as venlafaxine *versus* SSRIs and NARIs, no advantage in efficacy has been achieved relative to tricyclics.[2,3,37,38] Nonetheless, it would be premature to abandon monoaminergic mechanisms: several novel targets and mechanisms of potential importance remain to be clinically exploited (Table 4 and FIG. 2).

Triple inhibitors of monoamine reuptake

Currently used antidepressants generally interfere with transporter-mediated reuptake of 5-HT, NA, or both. Moreover, mainly due to actions at NA transporters, which control the levels of dopamine (DA) in the frontal cortex, they likewise reinforce frontocortical dopaminergic transmission.[3,39,40] Notably, without affecting extracellular levels of DA, sustained administration of diverse antidepressants and electroconvulsive therapy enhances transmission at dopaminergic receptors in the nucleus accumbens.[2,3,41] A generalized and rapid strengthening of dopaminergic transmission could otherwise be achieved by direct blockade of DA transporters, which are enriched in mesolimbic structures.[40] This is important, because a dysfunction of dopaminergic mechanisms of reward is incriminated in anhedonia.[41] Moreover, suppression of DA reuptake enhances sexual function and may improve cognitive performance.[3,42,43] Finally, the DA reuptake inhibitor (DARI) bupropion enhances the antidepressant actions of SSRIs in rodents and in humans,[44,45] so it is worth asking how antidepressants that interact with DA transporters in addition to 5-HT or NA transporters (or both) compare with associations of DA reuptake inhibitors and SSRIs and SNRIs (further discussed later in this review).

Based on this reasoning, and in view of the relative simplicity of designing drugs that inhibit DA reuptake, there is much current interest in triple inhibitors of 5-HT, NA, and DA reuptake that express antidepressant actions

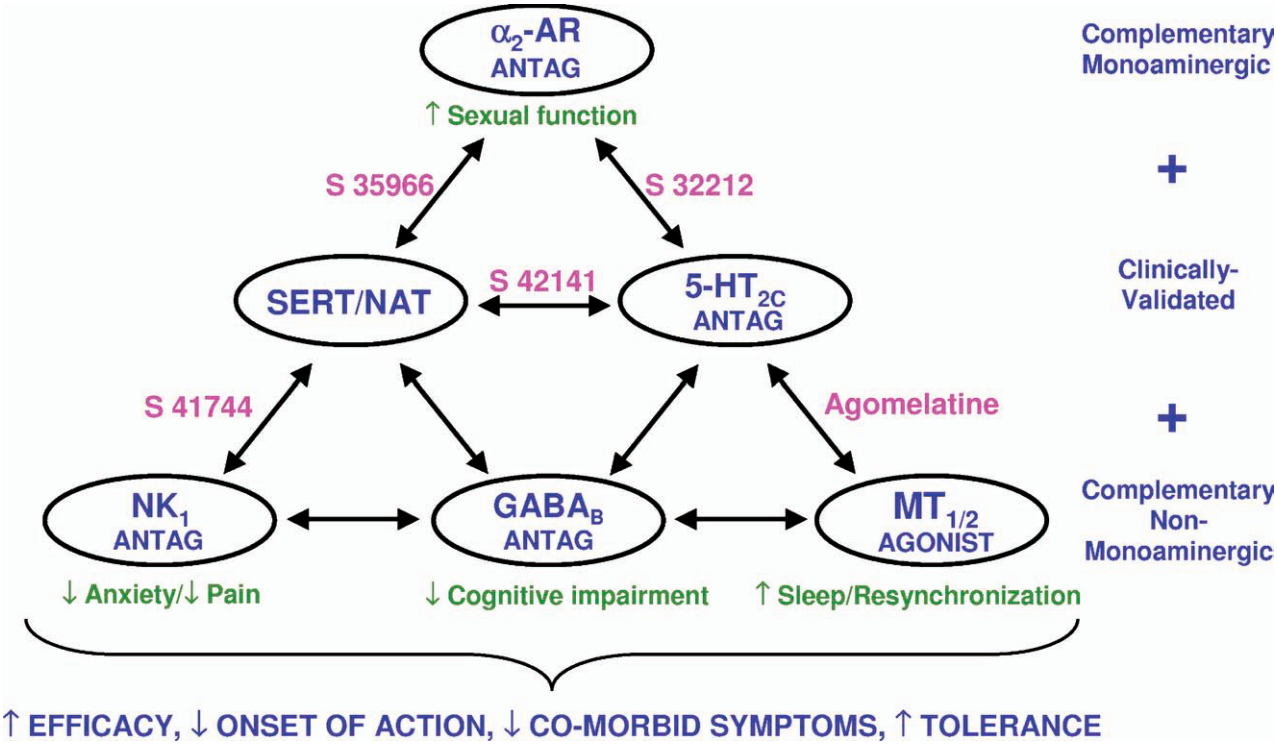

FIG. 3. A matrix of dual-acting agents for the improved treatment of major depression. One compelling strategy for improved drugs is to retain a clinically validated monoaminergic substrate of antidepressant activity and to build in complementary mechanisms: for example, additional monoaminergic actions such as blockade of α_2-adrenoceptors. A vast range of nonmonoaminergic targets could also be integrated, as illustrated with neurokinin$_1$ antagonism, GABA$_B$ antagonism, and agonism at melatonin receptors. In addition, it is theoretically possible to unite nonmonoaminergic mechanisms. Examples of bimodal monoaminergic/nonmonoaminergic antidepressants under study in the author's laboratory are given. Antag = antagonist; AR = adrenoceptor; 5-HT = serotonin; MT = melatonin; NAT = noradrenaline transporter; NK = neurokinin; SERT = serotonin transporter.

in behavioral models (FIG. 4).[46–51] In addition to possible autonomic and cardiovascular adverse effects, a concern with drugs blocking (mesolimbic) DA reuptake is their potential for abuse and likelihood of dependency. Nonetheless, the kinetics of elevation in DA levels is the key question, and drugs with slow rates of DA rise may be acceptable.[52,53] Initial experimental data are in line with this optimism, although rigorous clinical feedback is yet to come. It can be hoped that triple inhibitors will prove to have acceptable abuse and dependence potential and will offer improved efficacy in the management of depression—and perhaps also of other disorders, such as Parkinson's disease.[54]

Agents blocking both 5-HT reuptake and inhibitory 5-HT autoreceptors

Encouraging findings with adjunctive use of pindolol, a β-adrenoceptor (AR) partial agonist with 5-HT$_{1A/1B}$ antagonist properties, prompted the search for drugs behaving as either 5-HT$_{1A}$ antagonist/SRIs or 5-HT$_{1B}$ antagonists/SRIs (FIG. 5).[3,40,55–57] Although clinical confirmation is still pending, they can be expected to mimic the downregulation of 5-HT$_{1A/1B}$ autoreceptors seen upon long-term exposure to SSRIs, thereby relieving negative feedback and enhancing speed to efficacy.[58–61] However, few 5-HT$_{1B}$ antagonists/SRIs have seen the light of day, and mixed 5-HT$_{1A}$ antagonists/SRIs await comprehensive characterization *in vivo*.[5,57,62,63] Several 5-HT$_{1A}$ partial agonists with SRI properties have been described (FIG. 5), but despite evidence of 1) antidepressant actions in rodents, 2) enhancement of frontocortical levels of DA and NA, and 3) a postulated rapid desensitization of 5-HT$_{1A}$ autoreceptors, they are expected to blunt increases in 5-HT levels by SSRIs.[40,64] Indeed, clinical data on vilazodone (still in Phase III trials) have been disappointing.[65] Moreover, other agents such as EMD-95750 appear to have been dropped, and OPC-14523—which also recognizes σ_1-sites—has been shunted toward other indications, such as sexual dysfunction.[66,67]

A complementary approach consists of the generation of drugs acting as pan-autoreceptor antagonists that block 5-HT$_{1A}$, 5-HT$_{1B}$, and related 5-HT$_{1D}$ sites, which also have a minor presynaptic role (FIG. 5).[40,58,68] Such a triple-acting antagonist (or inverse agonist) might increase serotonergic transmission and display antidepressant effects in the absence of SRI properties—although this is a long shot, and such agents appear (at least for now) to be mainly of academic interest.[69,70] By contrast,

Table 4. *Comparison of Some Novel Bimodal and Trimodal Antidepressant Strategies under Evaluation*

Concept	Examples of Drugs	Clinical Aspects	Potential Advantages	Possible Drawbacks
Triple inhibition of 5-HT/NA/DA reuptake	SEP 225,289; GSK 372,475	Trials underway in major depression (and Parkinson's disease)	Improved efficacy, especially *vs* anhedonia; improved sexual function	Risk of dependence, abuse, psychosis
SRI and/or NA reuptake inhibition plus α_2-AR antagonism	S 39566; R 226121	The α_2-AR antagonist, yohimbine, enhanced clinical effectiveness of fluoxetine	Improved efficacy; faster onset; improved cognition and sexual function	Adverse cardiovascular effects (increased arterial pressure and tachycardia)
SRI plus histamine H_3 antagonism	JNJ 28583867	Selective H_3 antagonists under evaluation in Alzheimer's disease	Improved cognitive function; low risk of obesity	Poor sleep
SRI plus AMPA receptor facilitation	LY 392,098; LY 404,187*	Selective ampakines under study for cognition	Improved efficacy; enhanced neuronal resilience; improved cognition; resynchronization	Neurotoxicity, sensory disruption
SRI plus NK_1 antagonism	GSK 424,887	Vestipitant (NK_1 antagonist) + paroxetine (SSRI) under study	Improved efficacy; faster onset; control of somatic symptoms (nausea and pain) and of anxiety	Unclear (but less marked than for SSRIs)
SRI plus GR or CRF_1 antagonism	None described	Selective GR and CRF_1 antagonists under evaluation in psychotic depression	Increased efficacy (psychotic depression); enhanced resistance to stress; anxiolytic properties (CRF_1)	Excessive blockade of favorable actions of glucocorticoids/HPA axis
Melatonin agonism plus 5-HT_{2C} antagonism	Agomelatine	Proven short and long-term efficacy in major depression; effective in GAD	Diurnal resynchronization; improved sleep; lack of SSRI adverse effects	Few adverse effects overall, and mild; dizziness
SRI plus GSK-3β inhibition	None described	Lithium (GSK-3β inhibitor) enhances antidepressant efficacy of SSRIs.	Improved efficacy, enhanced neuronal resilience	Widespread CNS and peripheral nervous system effects (including metabolic)

5-HT = serotonin; CRF_1 = corticotrophin releasing factor$_1$; DA = dopamine; GAD = generalized anxiety disorder; GR = glucocorticoid; GSK-3β = glycogen synthase kinase-3β; HPA = hypothalamo–pituitary–adrenocortical; NA = noradrenaline; NK_1 = neurokinin$_1$; SRI = serotonin reuptake inhibition; SSRI = selective serotonin reuptake inhibitor.
*Bind (modestly) to 5-HT transporters.

SB-649915-B behaves as a mixed 5-$HT_{1A/1B}$ antagonist/SRI, with a more rapid onset of anxiolytic properties than with SSRIs (FIG. 5).[71–73] Its putative antidepressant profile remains uncertain and, like the ligands already discussed, SB-649915-B blocks postsynaptic 5-HT_{1A} and 5-HT_{1B} sites—which, rather awkwardly, may participate in the mood-improving actions of SSRIs.[3] Possibly, other components of depressive states such as cognitive deficits and sexual dysfunction will be improved by this intriguing drug.[3,42,60,74,75]

Although findings are less well established than for 5-HT_{1A} and 5-HT_{1B} autoreceptors, 5-HT_7 receptors may also be inhibitory to serotonergic transmission. Accordingly, 5-HT_7 antagonists enhance the actions of SSRIs and alone elicit modest antidepressant and anxiolytic effects in rodents.[76–79] Furthermore, mimicking SSRIs, genetic deletion of 5-HT_7 receptors suppresses rapid eye movement sleep.[80] Although the interrelationship between sleep and mood is the subject of debate, antagonism of 5-HT_7 receptors in the suprachiasmatic nucleus modifies circadian rhythms, which are deregulated in depression.[3,79,81,82] Hence, bimodal 5-HT_7 antagonists/SRIs are of interest. The 5-HT_{5A} receptors may also be inhibitory to serotonergic transmission, and 5-HT_{5A} sites in the suprachiasmatic nucleus also control circadian rhythms.[83] The recent description of selective 5-HT_{5A} antagonists, which enhanced frontocortical levels of 5-HT in the presence of 5-HT_{1A} receptor blockade, will allow for exploration of the potential interest of mixed 5-HT_{5A} antagonists/SRIs.[84]

Bimodal antidepressants acting as 5-HT_{2C} or 5-HT_{2A} receptor antagonists

Blockade of excitatory 5-HT_{2C} sites on GABAergic interneurons inhibitory to raphe cell bodies indirectly enhances the influence of SSRIs on levels of 5-HT in

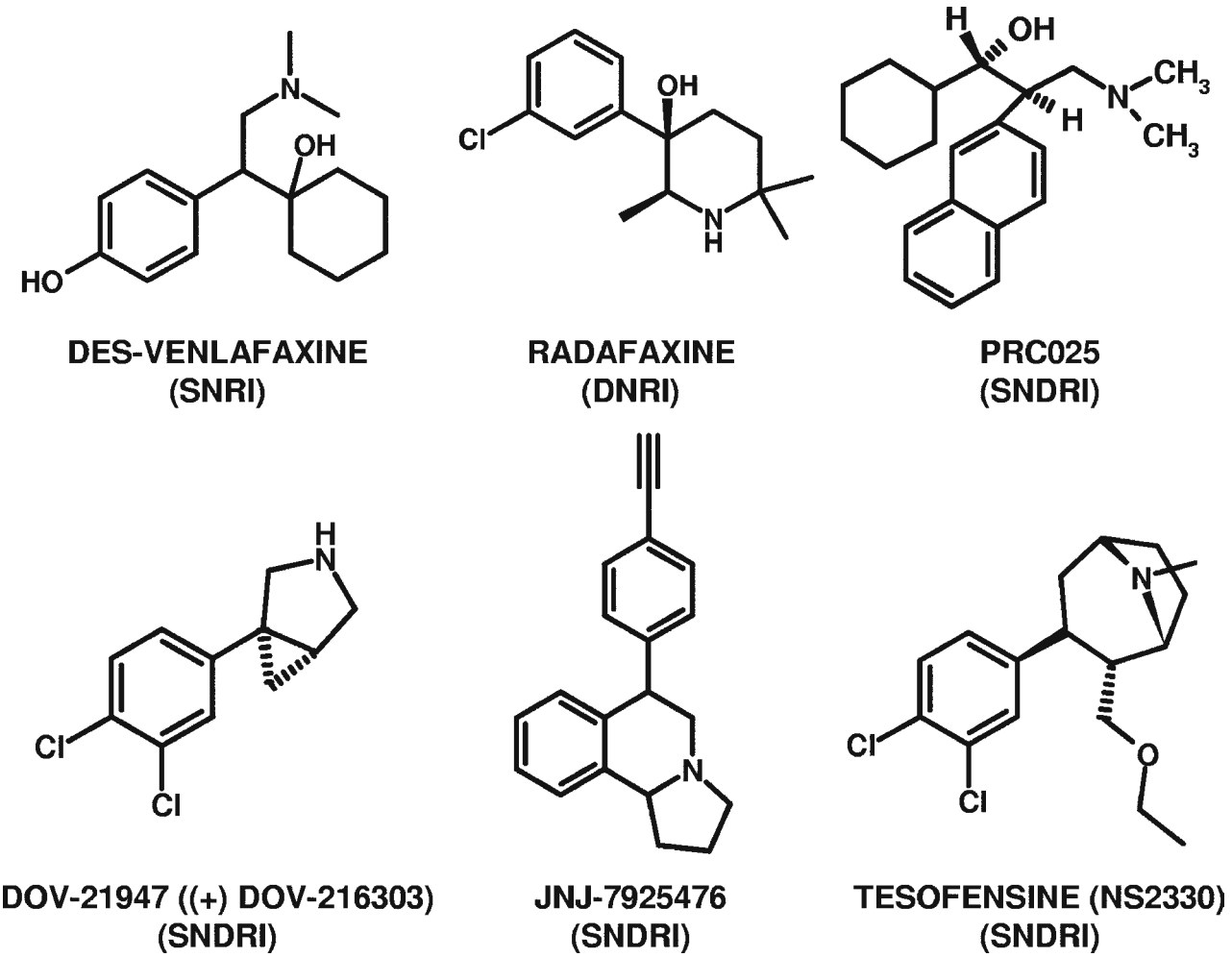

FIG. 4. Chemical structures of drugs interacting with various combinations of monoamine transporters. The 5-HT/NA reuptake inhibitor, des-venlafaxine, is an active metabolite of venlafaxine, while radafaxine (which suppresses transport of DA and NA) is an active (4-hydroxy) metabolite of the preferential DA reuptake inhibitor bupropion. PRC025 and DOV-21947 inhibit reuptake of 5-HT, NA and DA (SNDRI). The same holds for JNJ-7925476 and tesofensine, the latter of which is also oriented toward Parkinson's disease. Antag = antagonist; DA = dopamine; 5-HT = serotonin; NA = noradrenaline; DNRI = dopamine and noradrenaline reuptake inhibitor; SNDRI = serotonin, dopamine, and noradrenaline reuptake inhibitor.

frontal cortex and hippocampus.[85–87] In addition, blockade of ventrotegmental- and locus ceruleus-localized 5-HT_{2C} sites disinhibits dopaminergic and adrenergic pathways, respectively, and 5-HT_{2C} antagonists elicit robust antidepressant and anxiolytic actions in a broad range of paradigms.[40,85,86,88–90] Blockade of 5-HT_{2C} sites may, further, enhance sexual function and improve restorative slow wave sleep,[42,85,91] and antagonism of hypothalamic 5-HT_{2C} receptors facilitatory to the hypothalamo–pituitary–adrenocortical (HPA) axis abrogates its overstimulation by stress.[88]

Underpinning interest in drugs that both block 5-HT_{2C} sites and suppress 5-HT reuptake is the fact that, in addition to mediating anxiogenic actions, 5-HT_{2C} receptors are the principal culprits transducing the disruption of sleep, sexual function, and appetite by SSRIs.[3,85,90–93] Nefazodone has a 5-HT_{2C} antagonist/SRI profile but its blockade of H_1 receptors provokes sedation. Furthermore, nefazodone was found to be metabolically unstable and was withdrawn for concerns of hepatic safety, and similar drugs (e.g., YM-992) do not appear to have been pursued.[3,63] One attractive prospect would be a triple-acting 5-HT_{2C} receptor antagonist/SNRI corresponding to the core mechanism of tricyclic agents (but, obviously, shorn of their off-target effects at H_1 sites, muscarinic receptors, and cardiac ion channels) (FIG. 3).

Multitarget exploitation of 5-HT_{2C} receptor antagonism need not be confined to suppression of monoamine reuptake. A further promising avenue is represented by the urea derivative, S32212 (FIG. 6),[94,95] which has potent and balanced antagonist activity at 5-HT_{2C} and α_2-AR receptors and yet is devoid of affinity for H_1 receptors—distinguishing it from the tetracyclic mirtazapine, which elicits somnolence and obesity.[39,96–98] Integration of antagonist actions at α_2-ARs is of significance, because their blockade potentiates monoaminergic trans-

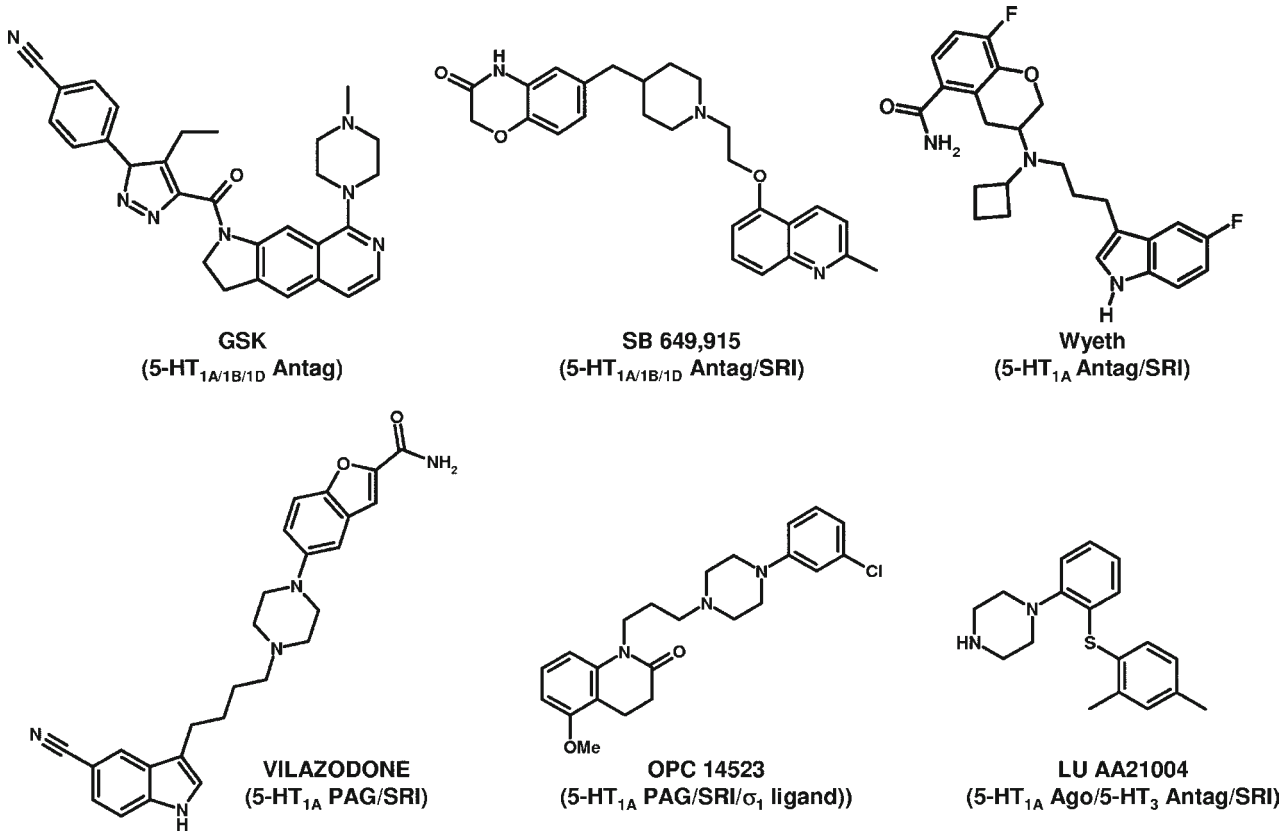

FIG. 5. Chemical structures of drugs acting at 5-HT autoreceptors inhibitory to serotonergic pathways, and with 5-HT transporters (SRI). A structure described by GSK behaves as a pan-antagonist at all classes of inhibitory 5-HT autoreceptor, although it does not bind to 5-HT transporters. Wyeth described a mixed 5-HT_{1A} antagonist/SRI (patent). SB 649,915 suppresses 5-HT reuptake and blocks 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} autoreceptors. Vilazodone suppresses 5-HT reuptake and is a partial agonist at 5-HT_{1A} receptors. OPC 14523 and LU AA21004 share these properties, but also interact, respectively, with σ_1 binding sites and 5-HT_3 receptors. Ago = agonist; Antag = antagonist; GSK = GlaxoSmithKline; 5-HT = serotonin; N = noradrenaline; PAG = periaqueductal gray area; SRI = serotonin reuptake inhibitor.

mission and is associated with modest antidepressant actions, as well as a beneficial influence on sexual behavior and certain components of cognitive function.[40,99–101] S32212 manifests antidepressant and anxiolytic properties in rodent models, and enhances cognition performance in some (but not all) procedures.[94,95]

Multitarget antidepressants homing into 5-HT_{2C} receptors agents may also profit from blockade of 5-HT_{2A} receptors, which blunts the disruption of hippocampal neurogenesis by stress and attenuates HPA axis overdrive.[3,58,102] Finally, antihallucinogenic properties of 5-HT_{2A} antagonists may be pertinent to the control of psychotic depression.[58,103]

Novel antidepressants with antagonist properties at 5-HT_3 receptors

Selective 5-HT_3 receptor antagonists are clinically important in the treatment of nausea, a prominent early adverse effect of SSRIs that may involve stimulation of peripheral 5-HT_3 receptors.[104,105] Furthermore, they exert modest antidepressant and anxiolytic effects in experimental procedures, and in an animal model ondansetron enhanced actions of SSRIs and SNRIs in a forced-swim test.[105–107] Accordingly, drugs with 5-HT_3 antagonist/SRI properties have attracted interest. Although litoxetine has disappeared from clinical databases, the recently disclosed triple-profile agent, Lu- AA-21004 (FIG. 5), which is a 5-HT_3 antagonist/5-HT_{1A} agonist/SRI, is in Phase III trials for treatment of major depression.[108]

Recruiting subsets of postsynaptic sites mediating beneficial actions of antidepressants

The identity of receptors implicated in the undesirable effects of monoaminergic antidepressants are fairly well known.[3,32] The 5-HT_{2C} (and 5-HT_{2A}) receptors contribute to the acute anxiogenic actions of SSRIs and to their inhibitory influence on sleep, sexual function, and appetite; the 5-HT_3 receptors are involved in the gastrointestinal effects and induction of nausea (see above). Stimulation of D_2 receptors can provoke nausea and hypotension, whereas D_3 receptors exert a negative influence on cognition,[32,34,109] and activation of α_1-ARs and β_1/β_2-ARs may perturb cardiovascular function.[32]

Somewhat paradoxically, although D_2 receptors transduce the positive influence of DA on mood, and

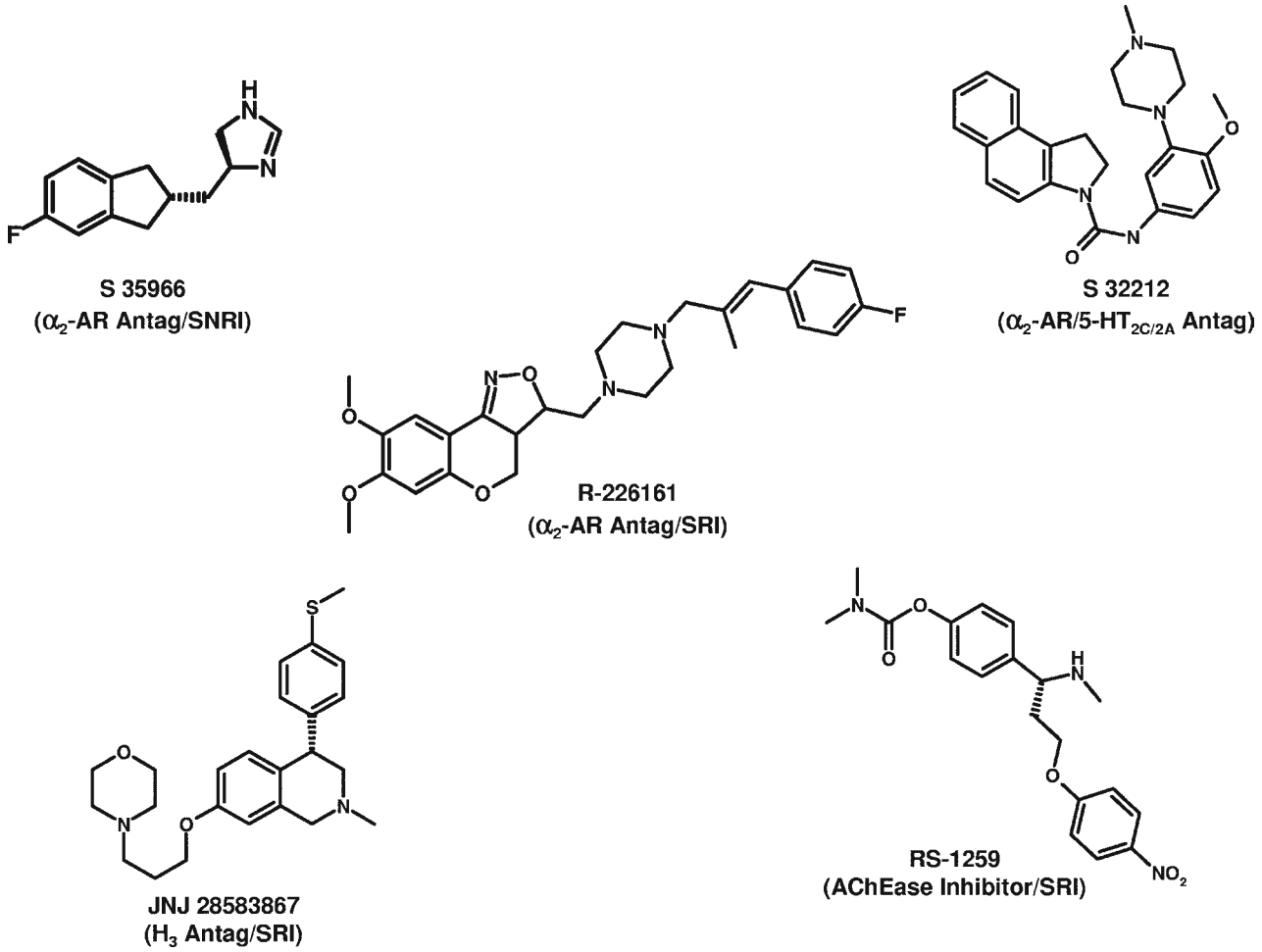

FIG. 6. Chemical structures of drugs acting at 5-HT transporters (SRI) and at various sites influencing cognition. S 35966 and R-226161 are antagonists at α_2-adrenoceptors and block the reuptake of 5-HT/NA and 5-HT, respectively. JNJ 28583867 is a mixed ligand of 5-HT transporters and Histamine H_3 receptors. RS-1259 blocks 5-HT reuptake and the activity of acetylcholinesterase. S 32212 is an antagonist at α_2-AR and 5-HT$_{2C/2A}$ receptors. Antag = antagonist; AR = adrenoceptor; H = histamine receptor; NA = noradrenaline; SRI = serotonin reuptake inhibitor; SNRI = serotonin and noradrenaline reuptake inhibitor.

D_1/D_5 receptors facilitate cognition, mechanisms mediating the beneficial effects of NA and 5-HT in depression remain uncertain.[3,41,43,110,111] α_1-ARs may well participate in the positive influence of NA on mood and cognition.[3,112] The β_1 and β_2-ARs are also involved.[113] Curiously, an agonist at β_3 receptors (essentially absent from healthy adult human brain, although data for depressed tissue do not appear to be available) was in development for depression, but was recently discontinued.[114,115]

As regards 5-HT, the traditional candidates are 5-HT$_{1A}$ receptors. This has never been clinically proven, not least owing to poor tolerability of agonists.[3,32]. Ligands acting *via* specific 5-HT$_{1A}$-recruited signaling pathways may offer the hope of future clinical exploitation.[68,116] 5-HT$_{1B}$ receptors have also been forwarded as mediators of antidepressant actions of SSRIs, together with 5-HT$_{2A}$ and (controversially) 5-HT$_{2C}$ and 5-HT$_6$ sites; 5-HT$_4$ receptors were also recently added to the inventory of potential serotonergic mechanisms for improving mood.[3,58,86,117–119]

No single receptor can account for the global therapeutic influence of antidepressants that increase monoamine levels. For example, cellular substrates controlling neurogenesis in the hippocampus differ from those that counter anhedonia. Monoaminergic antidepressants act, then, in a multitarget fashion. Once we have a better idea of exactly which postsynaptic sites genuinely contribute to, or interfere with, their favorable effects, it may be possible to conjure up dual- or triple-acting drugs acting *via* optimized subsets of receptors. In this regard at least, selective agents have an indispensable role in discerning the functional significance of individual classes of monoaminergic receptor.

Dual α_2-AR autoreceptor antagonists/monoamine reuptake inhibitors

Tonically active, inhibitory α_2-AR autoreceptors are found on the perikarya and terminals of adrenergic pathways, and α_2-AR heteroceptors are localized on terminals of corticolimbic serotonergic pathways and mesocortical dopaminergic fibers projecting to the frontal cortex.[40,100] Accordingly, the actions of antidepressants that increase extracellular levels of NA may be blunted by their indirect recruitment of presynaptic α_2-ARs, and gradual desensitization of α_2-AR autoreceptors is likely related to the delay to full efficacy.[36,40,100,120] Although not all data support this notion,[121] antagonism of α_2-ARs consistently enhances the induction of extracellular levels of monoamines by antidepressants.[40,100] This suggests that drugs that both block α_2-ARs and suppress 5-HT and/or NA reuptake may be powerful and rapidly active antidepressants (FIG. 6). Indeed, although α_2-AR antagonists display only weak, variable, and clinically trivial antidepressant properties, concomitant administration of yohimbine accelerated the therapeutic actions of fluoxetine.[122] Underpinning interest in agents with α_2-AR antagonist properties is the fact that blockade of inhibitory α_2-ARs on cholinergic terminals in frontal cortex potentiates both acetylcholine release and some (but not all) aspects of cognitive performance.[3,101,123] Finally, α_2-AR blockade may ameliorate sexual dysfunction and counter its disruption by SSRIs.[99]

Based on such considerations, several groups have designed centrally active agents that both antagonize α_2-ARs and suppress reuptake of 5-HT or NA (or both) *in vivo*.[124,125] For example, the spiroimidazoline α_2-AR antagonist/SNRI, S35966 (FIG. 6), elicits marked increases in frontocortical levels of NA, DA, and 5-HT, compared with SNRIs, is more potent in behavioral models of antidepressant activity, and it more rapidly downregulates 5-HT_{2A} receptors in frontal cortex, a cellular marker of therapeutic activity.[126] Moreover, in distinction to SNRIs, S35966 releases acetylcholine in frontal cortex, shows procognitive properties in a model of social recognition, and fails to perturb sexual function in rats.[126]

Although such findings are promising, the potential influence of α_2-AR antagonists/SNRIs on cardiovascular parameters remains a concern, given that sympathetic terminals likewise bear inhibitory α_2-ARs. Clinical experience with mianserin, a drug that blocks α_2-AR sites and NA reuptake, is reassuring; however, mianserin also exerts other actions (like α_1-AR blockade) that may compensate for excursions in circulating levels of NA.[3,32] Drugs such as RS221661 that block α_2-ARs and preferentially suppress 5-HT *versus* NA reuptake may be more acceptable.[125] In any event, it seems worth pursuing multifunctional α_2-AR antagonists plus 5-HT/NA reuptake inhibitors (and comparing their actions to drug combinations), because they may prove effective in patients resistant to or slowly responsive to currently used drugs.

HYBRID MONOAMINERGIC/NONMONOAMINERGIC ANTIDEPRESSANTS

Histamine H_3, nicotinic, and $GABA_B$ receptors as targets: improving cognitive function

Histamine H_3 receptors are an interesting target because they act as inhibitory autoreceptors on histaminergic neurons and exert a negative influence on frontocortical monoaminergic and cholinergic pathways; accordingly, selective H_3 antagonists have procognitive and modest antidepressant properties.[127–129] However, they are unlikely to be useful per se in depression, which suggests association with another clinically validated mechanism. Several structures interacting both with H_3 receptors and with 5-HT transporters were recently described, including JNJ-2583867 (FIG. 6), which increases extracellular levels of 5-HT in frontal cortex and is active in preclinical models of depression.[130,131] Dual-acting H_3 antagonists/SRIs represent a promising concept for improved control of mood and cognitive impairment in depression, with a low risk of obesity in view of the inhibitory influence of H_3 antagonists on appetite.[132] Nonetheless, one possible disadvantage is a possible interference with sleep, due to their wake-inducing actions (Table 4).

Stress-responsive cholinergic neurons also broadly influence mood and cognition.[3,133] Although muscarinic receptors should not be ignored, nicotinic sites are of particular interest, given that several classes of antidepressant, including fluoxetine (SSRI), reboxetine (NARI), and bupropion (DARI) and its active 4-OH metabolite, radafaxine, interact with various nicotinic receptor subunits.[3] It seems not unreasonable to imagine that optimized dual- and triple-acting nicotinic/monoaminergic antidepressants could be devised. The exact nicotinic receptor subunits to target and the optimal degree of drug efficacy is less obvious, because there is evidence that both partial agonists and/or antagonists at various subtypes of nicotinic receptor can improve mood.[3,133–136] Currently, the best evidence is that reducing activity of $\alpha_4\beta_2$ and, possibly, α_7 sites is related to antidepressant properties.[134,136] and the preferential $\alpha_4\beta_2$ antagonist mecamylamine enhances antidepressant actions of SSRIs in humans.[137] On the other hand, antidepressants with partial agonist actions at α_7-subunits may improve cognitive function. A further approach to improving cognition in depression is represented by RS-1259, which behaves as a mixed acetylcholinesterase inhibitor/SRI (FIG. 6).[138–140] Although originally intended for Alzhei-

mer's disease, its potential in geriatric depression justifies examination.

Many other multitarget approaches to improving cognition and mood in depression could also be cited, including drugs behaving as $GABA_B$ receptor antagonists, which should exhibit procognitive and antidepressant properties.[141–143] Indeed, $GABA_B$ antagonists enhance the influence of SSRIs on serotonergic transmission in the frontal cortex.[87,144,145]

Glutamatergic receptors as targets: ionotropic and metabotropic hypotheses

Glutamatergic transmission is responsive to stress, and it is perturbed in depressed states. Furthermore, both ionotropic (AMPA, kainate, and NMDA) and metabotropic (mGluR) I, II, and III receptors are implicated in the control of mood, cognition, circadian rhythms, motor behavior, and other functions perturbed in depression.[3,40,90,146–149] Blockade of hippocampal NMDA sites may help to protect neurons from deleterious consequences of excessive glutamate and glucocorticoid levels under protracted stress, and to abrogate the HPA overdrive seen early in depressed states.[150–152] NDMA receptor blockade yields antidepressant actions both singly and in association with SSRIs in rodents. Supporting interest in mixed NMDA agents/SRIs, the open channel blocker ketamine exerts rapid antidepressant properties in patients.[153–155]

Although the risk of cognitive impairment and psychosis tempers interest in channel blockers as a therapeutic strategy,[34,146,156] the anti-Alzheimer agent memantine has only a low risk of psychosis, because of its marked voltage-dependency and rapid kinetics[156–158]; its potential antidepressant actions are under investigation, although clinical data are as yet ambivalent.[159–161] In fact, memantine interacts with several other sites[156] (Table 2), supporting the notion that NMDA receptor blockers could serve as a template for generating well-tolerated multitarget antidepressants of accelerated onset of action. Multitarget drugs could also be constructed around structures specifically blocking NR2B NMDA receptor subunits or the colocalized $glycine_B$ sites, which should have a reduced risk of psychosis and other adverse effects.[146]

One theory of the antidepressant actions of NMDA antagonists suggests that they indirectly favor transmission at AMPA *versus* NMDA sites.[155] Correspondingly, positive allosteric modulators (ampakines) at AMPA receptors exert antidepressant properties, induce neurogenesis, and favor cognitive performance, both singly and in association with SSRIs.[148,162–164] An additional incentive to search for drugs with dual ampakine/5-HT reuptake-inhibiting properties is that stimulation of AMPA receptors (in the suprachiasmatic nucleus) may recoordinate circadian rhythms in desynchronized patients.[3,165] Furthermore, AMPA receptors are involved in antidepressant actions of lithium, which reliably potentiates SSRI efficacy in patients.[166] Drugs with joint ampakine/5-HT reuptake inhibitory properties could be highly effective antidepressant agents, with a favorable effect on cognition and, possibly, on diurnal rhythms of behavior. However, AMPA receptors are widely distributed, play an important role in sensory transmission in the dorsal horn, and—despite promoting neurogenesis—their stimulation is implicated (possibly along with glucocorticoids) in the neurodegenerative influence of chronic stress.[148,156,164,167] It will be necessary to establish that antidepressants acting at AMPA receptors neither disrupt sensory transmission nor exacerbate deleterious neuronal effects of sustained stress. The chemical feasibility of dual AMPA facilitators/SRIs is supported by observations that the ampakines LY392,098 and LY404,187 have significant affinity for 5-HT transporters (personal observation).

Several subtypes of mGluR receptor influence mood and HPA activity. For example, mGluR5 receptor antagonists show antidepressant and anxiolytic properties in rodents,[149] and low-efficacy agonists at mGluR2/3 sites accelerate adaptive changes elicited by chronic treatment with imipramine.[168] Although structure–activity relationships of orthosteric ligands are restricted, allosteric sites offer scope for generation of mixed mGluR/serotoninergic ligands for improved treatment of depression.

Neuropeptidergic receptors as targets: focus on Neurokinin$_1$ (NK_1) receptor antagonists/SRI

Genetic or pharmacological invalidation of NK_1 receptors has been shown to improve resistance to stress, to promote neurogenesis, and to be accompanied by antidepressant and anxiolytic effects in several (but not all) experimental procedures.[3,169,170] Acquisition of these data paralleled the therapeutic reorientation of selective NK_1 receptor antagonists into the psychiatric domain from the management of pain (where high expectations turned to major disillusion). Despite early clinical indications that discrete blockade of NK_1 receptors is associated with antidepressant and, possibly, anxiolytic actions, further studies questioned whether selective NK_1 receptor inactivation permits robust and consistent relief of depressed states.[170–172]

It would be naïve, however, to jump to the conclusion that NK_1 receptors are irrelevant. Rather, they should be exploited in a multitarget framework, as is reflected in current interest in the conjunction of NK_1 receptor antagonism with inhibition of 5-HT reuptake. This concept is of particular interest because blockade of NK_1 receptors promotes the activity of corticolimbic adrenergic and dopaminergic pathways, complementing the effects of 5-HT reuptake inhibition.[173–177] Blockade of NK_1 receptors also accelerates the long-term facilitatory influence of SSRIs on serotonergic transmission, possibly

by accelerating desensitization of inhibitory 5-HT_{1A} autoreceptors.[175–177] These observations suggest that dual agents may be both more effective and rapid-acting than SSRIs and, inasmuch as NK_1 antagonists enhance antidepressant actions of SSRIs yet curtail their anxiogenic effects,[3,177,178] they should be devoid of the symptoms of nervousness that patients may experience at the beginning of SSRI therapy.

Both SSRIs and NK_1 antagonists display anti-impulsive properties, and also blunt light-induced advances of circadian rhythms.[3,90,169,179–181] As regards tolerability, mixed NK_1 antagonists/SRIs should exert a less negative influence on sexual function and sleep than SSRIs and, in view of clinically proven antiemetic properties of NK_1 antagonists, they may provoke less nausea.[3,170–172,182] Accordingly, considerable attention is being devoted to drugs blocking both NK_1 receptors and 5-HT transporters. Pioneers in this regard were Ryckmans et al.[183] (structure UCB in FIG. 7), who showed that dual-acting agents are feasible despite the structural disparity between NK_1 receptors and 5-HT transporters.

These arguments should be kept in mind when assessing clinical data with other classes of highly selective neuropeptidergic agents. For example, NK_2 receptors may participate in the control of mood, and NK_2 antagonists were reported to have antidepressant actions, blunt the response to stress, and counter overdrive of the HPA axis.[3,184,185] Collectively, these data suggest utility in treating major depression. However, therapeutic effects of the selective NK_2 receptor blocker saredutant were not compelling, and it was discontinued. Despite the low density of NK_2 receptors in the brain (or at least the healthy brain), it seems justified to contemplate NK_2 antagonists/SRIs as potential antidepressants.

The selective vasopressin (V_{1b}) receptor antagonist, SSR149415, has been abandoned from clinical trials despite a solid experimental basis supporting its use in depression; more robust effects may be achieved when it is coupled to SRI properties.[186–188] In addition, notwithstanding experimental evidence for a role of galanin and melanin concentrating hormone in the regulation of mood and cognition, galanin receptor ligands and melanin concentrating $hormone_1$ receptor antagonists are conspicuously absent from current drug pipelines—although this may be related to difficulties in finding drugs with appropriate safety and pharmacokinetic profiles, not only to the issue of efficacy.[189,190] Finally, evidence supporting the relevance of central corticotrophin releasing $factor_1$ (CRF_1) receptors in the response to stress, control of the HPA axis, regulation of mood, and induction of anxious and depressed states is overwhelming, but clinical data with selective antagonists are frustratingly sparse, and the most recent report was negative.[3,90,191,192] For these (and other) neuropeptide receptors, association with SRI properties or other mechanisms controlling depressed states should be envisaged.

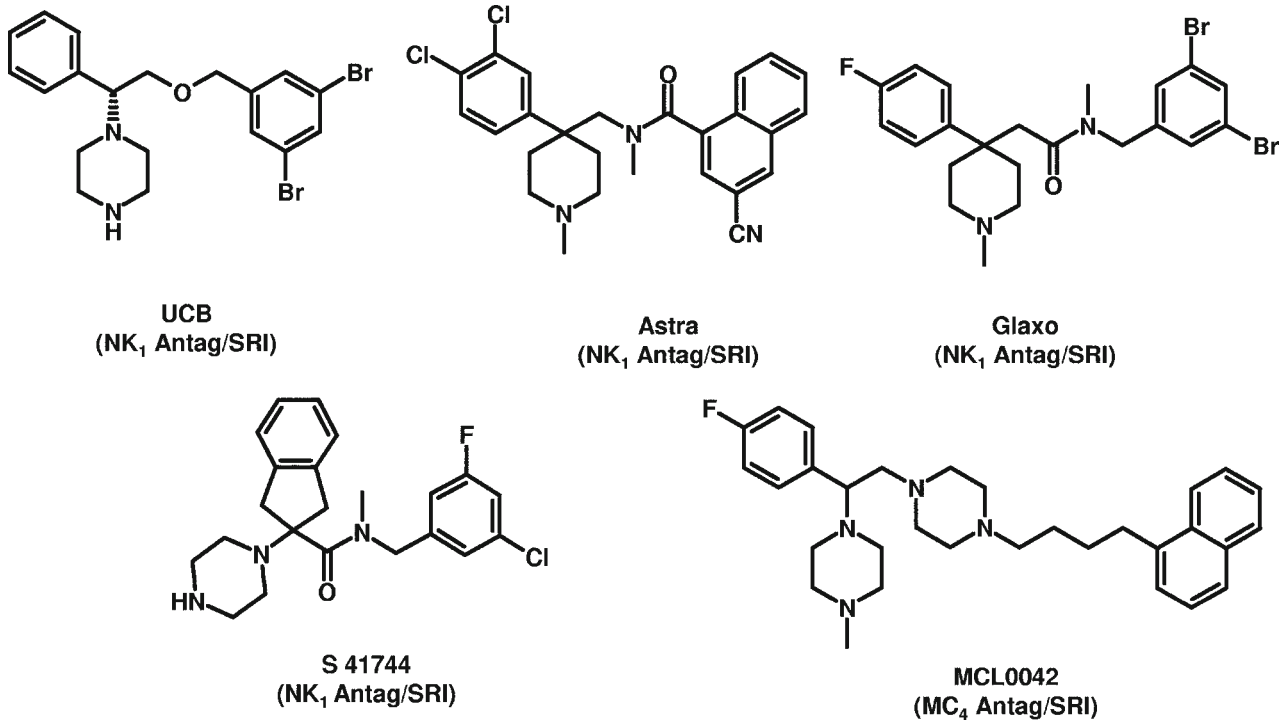

FIG. 7. Chemical structures of drugs that interact with both neuropeptidergic receptors and 5-HT transporters. UCB, Astra Zeneca (patent), GlaxoSmithKline (patent), and Servier (S 41744) have described drugs that act as antagonists at $neurokinin_1$ receptors and also suppress the reuptake of 5-HT (SRI). By contrast, MCL0042 acts as a combined antagonist at $melanocortin_4$ receptors and a blocker of 5-HT transporters. Antag = antagonist; MC = melanocortin; NK = neurokinin; SRI = serotonin reuptake inhibitor.

It must be emphasized that the goal of interlinking neuropeptide receptor antagonist and SRI properties is perfectly realistic. For example, in addition to NK_1 receptors/SRIs, MCL10004 both suppresses 5-HT reuptake and blocks melanocortin$_4$ receptors, a dual mechanism that may synergistically improve mood (FIG. 7).[193,194] Mixed ligands of neuropeptide Y_5 receptors and 5-HT transporters have also been described.[195]

The real future of neuromodulatory peptidergic mechanisms may well lie in the multitarget universe, and it is hard to comprehend the persistent obsession with selective agents only. To reiterate, disappointing results with a selective agent do not necessarily imply therapeutic irrelevance but, rather, invite exploitation by means of a multitarget strategy. For all novel targets, it would be wise to concomitantly pursue programs with both selective and multitarget agents. Furthermore, it would appear sensible to explore drug efficacy under a variety of conditions in specific subpopulations of patients, such as those with high stress-sensitivity or HPA axis overdrive, and both in naïve (i.e., never treated) subjects and those resistant to monoaminergic agents.

Innovative neuroendocrine mechanisms: calming HPA axis overdrive and recruiting melatonin receptors

Together with V_{1b} receptors, CRF_1 receptors comprise key mechanisms for recruiting the endocrine arm of the HPA axis. HPA overdrive under conditions of protracted, intensive, and uncontrollable stress contributes to the pathogenesis of depression and is accompanied by a negative influence on mood, cognition, and neural integrity due to excessive and disproportionate activation of cerebral glucocorticoid (GR) *versus* mineralocorticoid receptors.[3,167,196,197] Furthermore, HPA overdrive is correlated with poor responsiveness to SSRIs.[197] Glucocorticoid synthesis inhibitors such as metyrapone promote neurogenesis, display antidepressant actions, and potentiate the actions of SSRIs.[3,198,199] Furthermore, they accelerate antidepressant action of SSRIs in patients.[200,201]

Glucocorticoid antagonists attenuate the reduction of synaptic plasticity by stress, display antidepressant actions in rodents, and exert a positive influence on mood (and cognition) in association with SSRIs in psychotic depression, which is characterized by a pronounced overactivation of the HPA axis.[3,167,197,202–204] The beneficial effects of GR antagonists and metyrapone involve a sustained induction of mineralocorticoid receptors, as well as serotonergic and dopaminergic mechanisms.[3,196,197,199,205–207] Agents curtailing HPA overdrive may also abrogate deleterious somatic effects such as obesity, osteoporosis, and coronary artery disease.[3,196] Finally, GR antagonists hasten and augment the induction of 5-HT levels elicited by chronic fluoxetine, possibly by accelerating desensitization of 5-HT_{1A} autoreceptors.[208]

These observations support interest in combined inhibitors of 5-HT reuptake plus suppressors of glucocorticoid synthesis or GR receptor antagonists.[197,206] There are caveats, however: 1) clinical data remain in need of consolidation; 2) only certain patients, such as those with psychotic depression, may be sensitive to treatment, whereas others with atypical depression and seasonal affective disorder show blunted HPA axis activity; 3) the HPA axis is regulated around a set-point, so its activity should not be too strongly compromised;[3,167,196,197,206] and 4), it would prove challenging to integrate GR blockade and 5-HT reuptake inhibition into a single structure. Thus, despite the interest of calming HPA axis overdrive by dual-acting agents with SRI activity, further work is needed on this concept.

As with GR antagonists, it may prove hard to develop drugs with dual thyroxine activity/SRI properties, despite compelling evidence that T_3 supplementation improves the clinical profiles of SSRIs.[3,18,21,22]

Agomelatine, a combined melatonin agonist/5-HT_{2C} antagonist, more concretely illustrates the clinical promise of dual-acting antidepressants integrating neuroendocrine and monoaminergic mechanisms.[209–211] The importance of 5-HT_{2C} receptor blockade in the treatment of depression was outlined above, and melatoninergic agonism offers complementary advantages. Although melatonin (which is released from the pineal gland and acts *via* MT_1 and MT_2 receptors in the SCN) does not exert marked antidepressant properties per se, it improves sleep and reschedules perturbed circadian rhythms in insomniacs.[81,212–214] Such actions of agomelatine would be beneficial in depression, inasmuch as patients generally exhibit reduced sleep quality and are often desynchronized.[3,81,82]

Reflecting melatoninergic agonist and 5-HT_{2C} receptor antagonist actions, agomelatine is effective in experimental models of antidepressant and anxiolytic properties.[209,210,215,216] Agomelatine also counters the suppression by hippocampal neurogenesis by stress, and abrogates HPA axis activation and behavioral indices of depression.[217] Underscoring its chronobiotic properties, agomelatine recoordinates experimentally perturbed circadian rhythms and sleep in rodents.[3,211] Correspondingly, agomelatine displays short- and long-term antidepressant properties in patients and, in contrast to SSRIs and SNRIs, sexual behavior is preserved and sleep initiation and quality are improved.[209–211,218,219] Furthermore, agomelatine is active in severely depressed patients,[209–211,218,219] and studies underway should more clearly define its potential advantages relative to SSRIs in specific populations of depressed patients (e.g., those with seasonal affective disorder).

STRATEGIES FOR THE FUTURE? MULTIFUNCTIONAL AGENTS INTERACTING WITH INTRACELLULAR SIGNALS

Recent years have witnessed something of an infatuation with intracellular proteins as targets for novel antidepressants: such agents may sidestep some of the drawbacks of conventional drugs and (although this is speculative) may counter the destructive effects of stress on neuronal resistance and neuronal plasticity—nebulous terms, though seductive, that are conveniently left undefined. As has become customary, the emphasis has been on highly selective ligands, but this is something of a misnomer, considering the almost universal expression of proteins such as brain-derived neurotropic factor (BDNF) and protein kinase C (PKC). The idea of a drug target within neurons is not in itself radical, as exemplified by inhibitors of monoamine oxidase. The following examples illustrate the challenges and opportunities faced in exploitation of intracellular targets, and the potential advantages of drugs with dual mechanisms of actions.

Lithium, which is widely used in the control of bipolar disorder, enhances the therapeutic efficacy of antidepressants such as SSRIs.[3,9,220,221] A reinforcement of monoaminergic transmission, possibly related to a downregulation of α_2-ARs[222], as well as to AMPA receptor facilitation,[166] may participate in the mood-improving benefits of lithium supplementation. Nonetheless, improved understanding of the intracellular substrates of lithium action might allow for the design of lithium-mimics that avoid its adverse effects (Table 4).[223–225]

Notably, by both direct and upstream (indirect) actions, lithium interferes with the activity (phosphorylation status) of glycogen synthase kinase-3β (GSK-3β), a highly regulated, constitutively active, and ubiquitous modulator of many proteins which is itself deactivated by phosphorylation.[9,223–225] Whether GSK-3 exerts a negative influence on mood per se is unclear, but several classes of antidepressant phosphorylate (deactivate) GSK-3β, as does electroconvulsive therapy.[223–226] Furthermore, facilitation of the mood-improving actions of antidepressant by zinc may reflect an inhibitory influence on GSK-3β,[227] and GSK-3β inhibitors display antidepressant properties in rodent models.[228,229] Finally, suppression of the proapoptoptic properties of GSK-3β may be involved in the neuroprotective properties of lithium.[224]

A generalized shutdown of GSK-3β would be disquieting in view of its broad physiological role, for example, in energy metabolism. Indeed, selective GSK-3β inhibitors are unlikely to be pursued further in the clinic because of indications of limited tolerability.[225] Contrariwise, dual inhibition of GSK-3β plus 5-HT reuptake, for example, may permit a less radical reduction in GSK-3β activity and, correspondingly, an enhanced therapeutic margin. In addition, inhibitors may be preferentially active in structures where GSK-3β is putatively upregulated in depression. This is by no means certain, however, and clinical proof is awaited. GSK-3β (and upstream proteins such as PI-3 kinase and Akt) exemplify both the promise and the potential pitfalls of drugs aimed at broadly expressed intracellular targets.

Such promise and pitfalls are likewise illustrated by inhibitors of phosphodiesterase-4 (PDE-4), which prolongs the effects of adenylyl cyclase by protecting cAMP from degradation.[230] This mechanism is under investigation for diverse disorders, including depression. Indeed, there is experimental and clinical evidence for antidepressant (and procognitive) actions of the PDE-4 inhibitor rolipram, although tolerability is poor: for example, inhibition of PDE-4 in the limbic system and brainstem provokes anxiety and nausea, respectively.[3,230–232] Drugs directed at specific isoforms of PDE-4 should have more regionally specific actions and improved tolerability, but they are unlikely to offer a broadly effective mechanism for improving mood and cognition. PDE-4 inhibition could, thus, be associated with a complementary upstream mechanism that recruits adenylyl cyclase: for example, β-AR, 5-HT$_4$, or 5-HT$_6$ receptor agonism.[113,117,118,231,232] Such a dual-acting drug should mainly inhibit PDE-4 (and hence favor cAMP generation) in structures where β-AR, 5-HT$_4$ or 5-HT$_6$ receptors are stimulated. This would increase the therapeutic window and enhance both the efficacy and duration of agonist-mediated actions.

Other intracellular modulators controlling mood could also be cited, such as 1) neuronal nitric oxide, which is recruited by NMDA receptors and interacts with 5-HT transporters,[3,146,233,234] or 2) σ_1 sites, which also interact with NMDA receptors and modulate intracellular Ca^{2+} availability.[3,235–237]

To reiterate, multitarget approaches appear more promising than selective agents for manipulation of intracellular proteins—not least, because they can help vector drug actions to cerebral areas involved in the induction and control of depression. Nonetheless, if antidepressants are designed to act *via* intracellular mechanisms, then it must be established how to monitor their effects in humans.

GENERAL DISCUSSION AND OPEN QUESTIONS

Chemical challenges in the design of multitarget agents

Challenges inherent in the design of selectively nonselective or designed multitarget agents should not be underestimated whether the goal is to 1) eliminate unwanted activities from a template involving multiple components of action, 2) to integrate a novel action into

a skeleton displaying one of two desirable features, or 3) to start from scratch by introducing two actions into a chemically original fragment.[3,10–15,238–241]

Although spacers are one option for linking two apparently incompatible pharmacophores, they need to be progressively removed in the search for overlapping elements. This is important, because maintaining a small size, modest lipophilicity, and a limited polar surface is compatible with a multitarget profile and critical for appropriate pharmacokinetic properties such as solubility and activity upon oral administration. Structure–activity relationships are hard enough to optimize for single sites, and they are commensurately more difficult when a balance is to be achieved between two or more actions. Nonetheless, as a rule of thumb, theoretical arguments and practical experience indicates that modest affinities at each site for a dual-acting agent are adequate, compared with high potency with a selective agent.

Other potential challenges for racemic structures are the risk that the two components of action differentially segregate among optically pure isomers. Furthermore, there is the potential problem that metabolites do not retain an appropriate multitarget profile. Finally, characterization of drugs with multiple mechanisms of action is more complex, more time-consuming, and more subtle than for selective agents, not least in the attribution of specific desired and undesired actions to individual pharmacological mechanisms. Concepts need to be carefully validated, and there remains the ineluctable question of the ideal ratio of activities—something that is invariably difficult to define, and even harder to systematically realize.

Despite these challenges, based on accumulating experience and the advent of new and powerful tools for analyzing and (tentatively) predicting drug polypharmacology, one may be optimistic that medicinal chemists will continue to progress toward the successful design of multitarget agents.[3,10–15,238–246]

Comparison of multitarget agents to drug associations

In advocating drugs with dual mechanisms of activity, an obvious question arises of how they compare to drug associations—that is, to mixtures of two or more compounds, either within a single treatment form (usually tablet) or given as a mixture.[244,247,248] The various advantages of multitarget drugs may be summarized as follows.[3]

First, effects of drug mixtures are not invariably the same as those of drugs with multiple mechanisms of action. Furthermore, although associating drugs might realistically reproduce the effects of drugs with dual mechanisms of action, this is increasingly unlikely for triple-acting drugs or for those with even more mechanisms of action.

Second, to develop drug mixtures, it is desirable to establish optimal drug doses (exposure) both separately and together, an onerous process.

Third, it is likewise necessary to undertake pharmacokinetic, safety, and galenic studies both on drugs alone and on their association, further complicating development.

Fourth, it is hard to predict the exact nature of interactions among drug mixtures, and the problem of interactions with other drug classes is even more challenging than for a single agent.

Fifth, compliance is a major problem in depression and other CNS disorders and is unlikely to be favored by multiplying the number of tablets to be taken.

Sixth, non–evidence-based polypharmacy is worryingly common for psychiatric disorders. It has been strongly challenged and is generally discouraged. Thus, it is difficult to promote the use of drug mixtures.

Seventh, for drugs to be combined they must present similar pharmacokinetic profiles. There is little sense in associating drugs with radically different half-lives.

Eighth, drug combinations necessitate considerable experience with the individual agents separately, and cannot be easily envisioned for mechanisms where clinical feedback is minimal or lacking. In certain cases, the relevant selective agent may simply not exist.

Ninth, multitarget drugs offer greater flexibility and opportunities from the point of view of intellectual property in terms of novel chemical structures and multiple mechanisms of action. Moreover, patents on novel drugs are far more robust than use patents and association patents, especially when the latter taken on agents previously patented by other institutions.

Finally, clinical testing and use of drugs from two different sources (e.g., two different pharmaceutic firms) is complicated, even if either or both are available as generics.

Nonetheless, the core point remains: the likely therapeutic benefits of multiple mechanisms of antidepressant action. In certain cases, drug combinations may well be warranted. For example, there is a limit to how many pharmacophores can realistically be introduced into a single structure, and chemical constraints complicate the design of certain classes of putative multitarget agent, such as mixed GR antagonists/SRIs. Furthermore, however challenging, drug combinations in theory permit the clinical definition of optimal ratios of activity for two complementary mechanisms, whereas the ratio is invariant for a dual-acting agent. It may also be possible to adapt combinations of specific drugs to the particular genetic and clinical profiles of individual patients, although this could prove problematic and should not be performed on an ad hoc basis. Economic considerations may also come to the fore, should the use of generic

associations prove substantially cheaper than novel multitarget agents of equivalent efficacy.

Thus, from a pathophysiological, conceptual, and clinical point of view, concomitant treatment with two well-characterized mechanisms should not be neglected, especially where they can be integrated into a single treatment (e.g., tablet).[248] Specific examples of drug combinations include a paroxetine (SSRI) plus vestipitant (NK_1 antagonist) formulation, and fluoxetine (SSRI) plus olanzapine (atypical antipsychotic).[20,177]

Network concepts of CNS function and dysfunction: the need for early intervention

Mood, cognition, and other functions disrupted in depression are emergent properties of overarching cerebral circuits, rather than of individual proteins, receptors, or neurons. The brain—its organization, operation, perturbation and treatment—is best understood in terms of functional modules and networks at a hierarchy of scales: from receptors, G-proteins, and their postsynaptic partners to neuronal circuits to regions such as the frontal cortex.[3,249–256] Mimicking other nonrandom networks, such as ecosystems, and reflecting the redundancy and differential responsiveness of numerous mechanisms controlling mood,[3,257–259] the brain is rather resistant to stress. Nonetheless, when stress (especially if multiple, intense, and/or protracted) disrupts brain networks, consequences can be serious (major depression being the example under consideration).[3,253,260–263]

As already stressed, drugs acting at key modes (hubs) such as 5-HT_{2C} receptors can be useful. However, mirroring the multitarget operation of the brain, drugs acting at several hubs or at multiple weak links may more effectively restore dysfunctional networks.[3,10–15,57,240,241] Furthermore, because phase-shifts to pathological states cannot easily be reversed (hysteresis), it is important to act with immediacy and even preventatively[3,4,16] (FIG. 8): hence the key importance of biomarkers for incipient depressed states.

These principles of network-based, multitarget, and (by preference) early intervention apply to other complex CNS disorders such as fibromyalgia,[264] bipolar disorder,[265] Parkinson's disease,[266,267] and Alzheimer's dis-

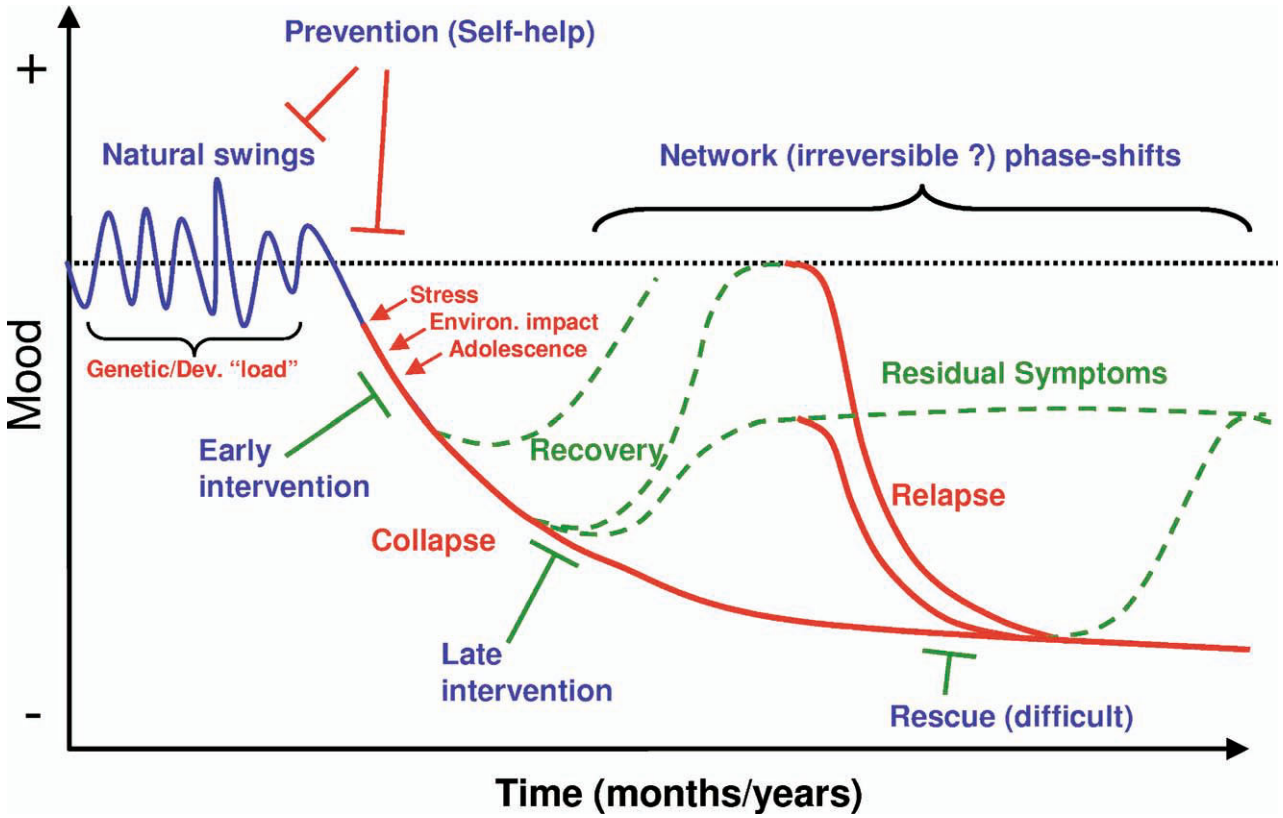

FIG. 8. The life-cycle of major depression and its treatment. Mood and its perturbation is under the influence of many, interacting genetic, epigenetic and developmental factors ("load"). Preventive strategies (often "self-help") help maintain equilibrium during natural swings in mood and in the face of threats to homeostasis. Such environmental challenges encapsulated under the term *stress* can be especially dangerous during adolescence and young adulthood. Because networks controlling mood may phase-shift into a new configuration that is hard to reverse (hysteresis), early treatment of incipient depressed states is crucial, whether by pharmacotherapy, other approaches, or both. Such treatments are also important as long-term strategies for countering residual symptoms and reducing the risk of relapse. Once well-established, and after multiple relapses, depressed states are hard to treat. These arguments apply not to only to dual- and triple-acting agents but to all classes of therapy.

ease,[268,269] as well as somatic disorders such as cancer, AIDS, and malaria.[270–274]

A valedictory caveat

Antidepressants with multitarget mechanisms are not synonymous with superior or better-tolerated antidepressants, as is exemplified by the off-target actions of tricyclic agents. Moreover, the benefits of certain dual-acting drugs, relative to single-target alternatives, are not spectacular. SNRIs show greater efficacy than SSRIs overall, and have a broader therapeutic range (e.g., against neuropathic pain), but their advantages are not dramatic and may be offset by other factors, such as an enhanced risk of hypertension.[3,35,37,38,275] In fact, rather inconveniently, the SSRI escitalopram appears to be equivalent in efficacy to SNRIs—although perhaps reflecting its distinctive multisite interaction with 5-HT transporters.[276,277] By analogy, mirtazapine (which has antagonist properties at α_2-ARs, 5-HT_{2C}, and 5-HT_3 receptors) is more effective than selective α_2-AR or 5-HT_3 antagonists, but it remains unknown how it compares with a selective 5-HT_{2C} antagonist in the clinic.[3,85,97] In addition, the benefits of mirtazapine are compromised by potent histamine H_1 antagonism.

There is much room for improvement on currently available multitarget drugs. Careful validation of innovative concepts and thorough drug characterization will be critical for improving efficacy and tolerability in the next wave of dual- and triple-acting antidepressants.

CONCLUSION

In light of the heterogeneity and multifactorial origins of depression, it is debatable whether its diversity of core and comorbid symptoms can be rapidly and efficaciously relieved, in a majority of patients and with minimal undesirable adverse effects, by drugs acting at a single site—and no multitarget mechanism is likely to fulfill this (illusory?) goal, either. Nonetheless, network-impaired dual, triple-acting and higher-order multitarget drugs appear to offer the best hope for the improved control of affective disorders by pharmacotherapy.

In this light, the bimodal and trimodal concepts discussed in this review address both common and contrasting features of depressed states. These strategies should then be considered as complementary and, in the absence of clinical data, it would be premature to come to any definitive conclusions on their relative merits. Only imaginative and rigorous clinical trials can provide compelling answers to such questions.

Finally, the significance of complementary (and validated) nonpharmacological treatments for prevention and treatment of depression must not be neglected. As discussed elsewhere,[34] multitarget agents will likely find their optimal use within the framework of a broader program of drug-based and non–drug-based strategies for controlling and preventing depressed states.

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