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Creating more effective antidepressants: clues from the clinic

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Antidepressant medications have eased the suffering of millions of people. In addition to treating depression, antidepressant drugs also treat several anxiety disorders. Unfortunately, there are problematic limitations with antidepressant agents, including a delayed therapeutic response and insufficient efficacy. Emerging evidence shows that atypical antipsychotic agents can be used as augmentation therapy in patients with poor responses to antidepressants. Future drugs combining key features of antidepressant and atypical antipsychotic agents could offer new promise for patients suffering from obsessive–compulsive disorder, post-traumatic stress disorder, panic disorder, generalized anxiety disorder and depression.

Introduction

In addition to major depressive disorder (MDD), antidepressants (e.g. selective serotonin-reuptake inhibitors (SSRIs)) are used to treat several psychiatric disorders, including obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder (PD) and generalized anxiety disorder (GAD). Unfortunately, the full therapeutic efficacy of these compounds can take several weeks to develop. Another major shortcoming of antidepressant drugs, in addition to a delayed onset, is limited efficacy. Not all patients show adequate responses to these medications, and, even for patients with partial responses, residual symptoms can cause intense suffering. Although the introduction of transfected cell lines has revolutionized the development of highly selective agents against well-defined targets, it has been difficult to predict which receptors might influence these shortcomings of antidepressant drugs. A recent article in *Drug Discovery Today* [1] reviewed strategies for producing antidepressants with a more rapid onset of action. The present article will review new clinical strategies using atypical antipsychotic agents to augment the responses to antidepressant agents. These clinical trials give some indication that the proportion of refractory patients and the antidepressant lag-time can both be reduced.

Atypical (or second-generation) antipsychotic agents (e.g. risperidone and quetiapine) differ from typical (or first-generation) antipsychotic agents (e.g. haloperidol), in that they produce a lower rate of neurological adverse events, such as extrapyramidal symptoms (EPS) or tardive dyskinesia. In addition, some atypical antipsychotic agents do not produce problematic elevations in prolactin levels (e.g. olanzapine). The atypical antipsychotic agents show good efficacy in treating the psychotic (e.g. hallucinations and delusions) and negative (e.g. lack of emotion, interest or expression) symptoms of schizophrenia, with clozapine and olanzapine potentially showing the greatest efficacy [2,3]. However, new problematic adverse events have come to the forefront with these atypical antipsychotic agents, including weight gain and dysregulation of glucose and lipid metabolism. Despite these limitations, several of these atypical antipsychotic agents (Figure 1) have been used to augment the actions of antidepressants in various psychiatric disorders. Results of clinical trials using atypical antipsychotic agents as augmentation agents for antidepressant treatment are summarized in Table 1. Judicious examination of the results of these trials provides clues (rather than definitive proof) to which receptors might usefully be blocked in the development of new classes of antidepressant agents with improved efficacy profiles over existing therapies. Although many of the trials discussed in this review are open label (and would not stand up to rigorous regulatory scrutiny), the findings can help us to identify good candidate activities for novel antidepressant agents. Definitive proof of these novel agents would come from rigorous clinical trials.

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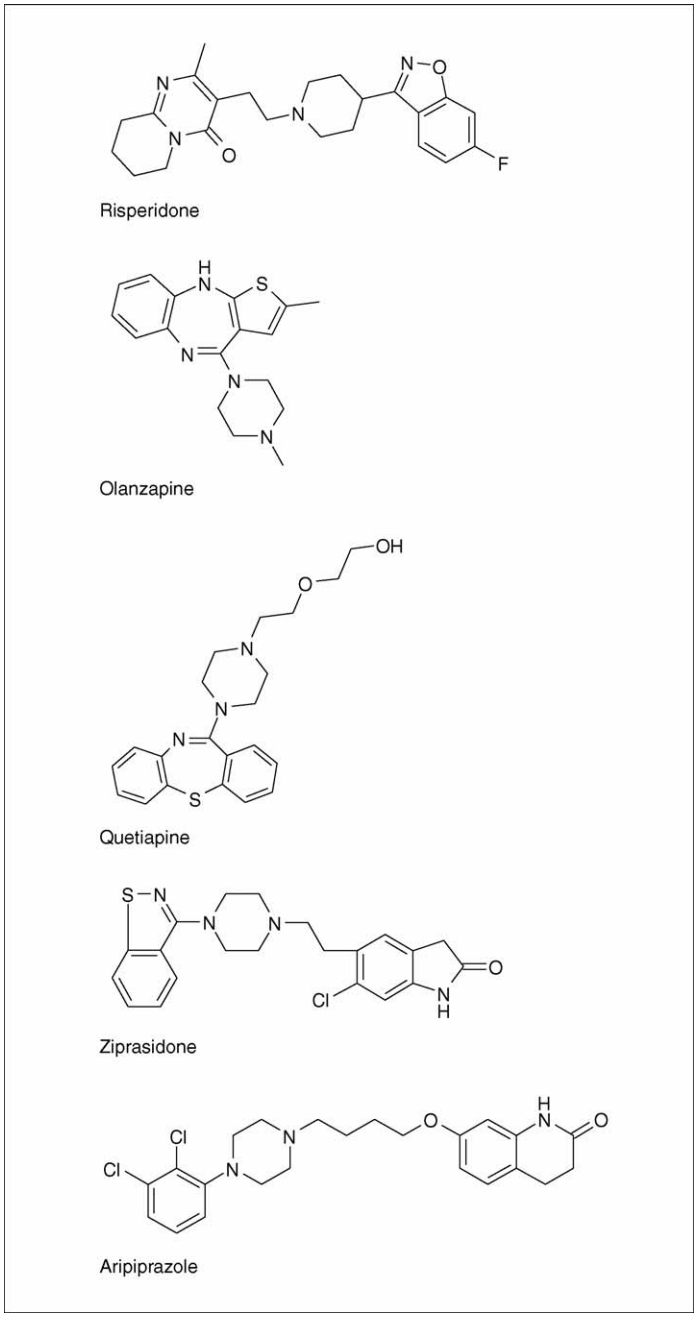

FIGURE 1

A selection of atypical antipsychotic agents. The structures of the atypical antipsychotics discussed in this article are pictured here. The compounds come from diverse structural series and have very rich pharmacologies (Table 2).

Clinical data

Major depressive disorder

As many as one in eight people will be treated for depression at some point in their lives [4]. Symptoms of depression include depressed mood, feelings of worthlessness or excessive guilt, fatigue, significant changes in weight, sleep disturbances and suicidal ideation. Unfortunately, 20–40% of patients will have less than a 50% reduction in symptoms in response to their first treatment with an antidepressant [5]. For patients with an inadequate response to an antidepressant, treatment options include switching to other antidepressants of the same class, switching to other antidepressants of different classes, augmentation with other pharmacological agents, electroconvulsive therapy and vagal nerve stimulation [6]. Early reports of the effectiveness of some typical antipsychotic agents in treating depression [7], and more recent reports of the beneficial effects of atypical antipsychotic agents on depressive symptoms associated with schizophrenia [8,9], prompted the study of atypical antipsychotics as augmentation agents for treating depression.

Risperidone. Case reports of the positive effects of augmenting the action of several antidepressants with risperidone for depression surfaced as early as 1998 [10,11]. One open pilot study reports that the combination of risperidone and the SSRI fluvoxamine from the beginning of antidepressant treatment enhances the therapeutic response rate [12]. No double-blind placebo-controlled studies of risperidone in augmenting the actions of antidepressants in depression are available at this time. Importantly, in almost all cases, low doses of risperidone (e.g. 0.5–1.0 mg) were used to augment the effects of antidepressant drugs; these doses are below the typical antipsychotic dose range (which is 2–6 mg). Normally, 'low' doses of all of the atypical antipsychotic agents are used for augmenting the effects of antidepressants. These low doses offer important clues as to their mechanism(s) of action as augmentation agents, as will be discussed later.

Olanzapine. A double-blind placebo-controlled study of the addition of olanzapine to depressed patients unresponsive to fluoxetine treatment showed that the combination had superior efficacy for treating resistant depression compared with either agent alone [13]. One of the more remarkable benefits of olanzapine augmentation reported in this study was the rapid rate (within one week) of improvement. Later, a 76-week open-label study showed that a combination of olanzapine and fluoxetine produced a rapid, robust and sustained improvement in patients with MDD and treatment-resistant depression [14]. Another open-label study showed that the addition of olanzapine to SSRI-resistant depressed patients increased slow-wave sleep and sleep continuity [15]. These effects on sleep are apparent after the first dose of olanzapine and might be a relevant mechanism in the therapeutic effects of olanzapine augmentation in SSRI-nonresponders. Another double-blind study examined the effects of combined treatment with olanzapine and fluoxetine in patients that had not responded to both an SSRI and the noradrenaline reuptake inhibitor nortriptyline. In these highly treatment-resistant depressed patients, combined therapy with olanzapine and fluoxetine showed a rapid, robust and sustained antidepressant effect [16]. Again, in almost all cases, low doses of olanzapine (e.g. 5–10 mg) were used to augment the effects of antidepressant drugs, these doses are below the typical antipsychotic dose range (which is 15–20 mg).

Quetiapine. A preliminary report showed that quetiapine was an effective augmentation agent for recalcitrant anxiety symptoms in patients treated with SSRIs for depression or anxiety [17]. In this study, improvement in symptoms was evident in the first week of augmentation. The mean quetiapine dose was 180 mg, which is below the typical antipsychotic dose (400–800 mg). Results from double-blind tests with quetiapine are not yet available.

Ziprasidone. In an open-label study, ziprasidone was used as augmentation for six weeks in SSRI-resistant depressed patients

TABLE 1

Summary of clinical trials using atypical antipsychotic agents to augment the efficacy of antidepressants

Disease	Antipsychotic	Antidepressant[a]	Trial type	Result	Ref.
Major depressive disorder	Risperidone	Fluvoxamine	Open-label	Enhanced response rate	[12]
	Risperidone	Multiple classes	Retrospective chart review	Improvement	[25]
	Olanzapine	Fluoxetine	Double-blind, placebo-controlled	Rapid improvement	[13]
	Olanzapine	Fluoxetine	Open-label	Rapid and sustained improvement	[14]
	Olanzapine	Multiple SSRIs	Open-label	Rapid improvement in sleep	[15]
	Olanzapine	Fluoxetine	Double-blind	Rapid improvement	[16]
	Olanzapine	Multiple classes	Retrospective chart review	Improvement	[25]
	Quetiapine	Multiple SSRIs	Open-label	Improvement in anxiety and depression	[17]
	Quetiapine	Multiple classes	Retrospective chart review	No improvement	[25]
	Ziprasidone	Multiple SSRIs	Open-label	Rapid improvement	[18]
	Ziprasidone	Sertraline	Open-label	Non-significant improvement	[19]
	Ziprasidone	Multiple classes	Retrospective chart review	No improvement	[25]
	Aripiprazole	Multiple SSRIs	Open-label	Improvement in anxiety symptoms	[20]
	Aripiprazole	Multiple SSRIs	Open-label	Improvement	[21]
	Aripiprazole	Multiple SSRIs, venlafaxine, buproprion	Open-label	Improvement	[22]
	Aripiprazole	Multiple SSRIs	Retrospective case review	Improvement	[23]
	Aripiprazole	Multiple SSRIs	Retrospective case review	Improvement	[24]
Obsessive–compulsive disorder	Risperidone	Multiple SSRIs, clomipramine	Open-label	Improvement	[28]
	Risperidone	Multiple SSRIs	Double-blind, placebo-controlled	Improvement	[29]
	Risperidone	Multiple SSRIs	Double-blind, placebo-controlled	Improvement	[30]
	Risperidone	Fluvoxamine	Double-blind, placebo-controlled	Improvement	[31]
	Olanzapine	Multiple classes	Open-label	Improvement	[32]
	Olanzapine	Multiple SSRIs	Open-label	Improvement	[33]
	Olanzapine	Fluoxetine	Open-label	Improvement	[34]
	Olanzapine	Fluoxetine	Double-blind, placebo-controlled	No improvement	[35]
	Olanzapine	Multiple SSRIs	Double-blind, placebo-controlled	Improvement	[36]
	Quetiapine	Multiple SRIs	Single-blind, placebo-controlled	Improvement	[37]
	Quetiapine	Multiple SRIs	Open label	Improvement	[38]
	Quetiapine	Multiple SRIs	Open label	No improvement	[39]
	Quetiapine	Multiple SRIs	Open label	No improvement	[40]
	Quetiapine	Multiple SRIs	Double-blind, placebo-controlled	Improvement	[41]
	Quetiapine	Multiple SRIs	Double-blind, placebo-controlled	No improvement	[42]
Post-traumatic stress disorder	Risperidone	Multiple classes	Double-blind, placebo-controlled	Improvement	[44]
	Risperidone	Multiple classes	Double-blind, placebo-controlled	Improvement	[45]
	Olanzapine	Multiple SSRIs	Double-blind, placebo-controlled	Improvement	[46]
Generalized anxiety disorder	Olanzapine	Fluoxetine	Double-blind, placebo-controlled	Improvement	[47]
Panic disorder	Olanzapine	Multiple SSRIs	Open-label	Improvement	[48]

[a] Abbreviations: SRI, serotonin-reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor.

[18]. In this study, 50–62% of the patients responded and 25–39% remitted. The mean daily dose of risperidone was 82.1 mg, well below the typical antipsychotic dose range (100–160 mg). The results from another open-label pilot study suggested that adjunctive use of ziprasidone in sertraline-nonresponders was more effective than continuation of sertraline monotherapy [19].

Aripiprazole. Several preliminary studies have examined the effects of adjunctive aripiprazole in a mixed population of patients with incomplete responses to antidepressants. Two

open-label studies showed aripiprazole to be an effective augmenting agent in depressed patients treated with SSRIs [20,21]. Another open-label study showed aripiprazole augmentation of multiple antidepressants (SSRIs, venlafaxine and buproprion) in treatment-resistant MDD [22]. Interestingly, in this study, motor adverse-events (i.e. akathisia) were observed if the starting dose of aripiprazole was too high. A retrospective case review reported that patients with depression and anxiety disorders with incomplete responses to SSRIs benefited from augmentation with aripiprazole [23]. In addition, another retrospective chart review reported on the effects of aripiprazole augmentation in treatment-resistant depression for patients who had already failed augmentation with at least one other atypical antipsychotic agent. In these highly treatment-resistant patients, there was a long-term net response rate of 27% [24].

Comparison of augmentation therapies. A retrospective chart review compared the effectiveness of olanzapine, risperidone, quetiapine and ziprasidone as augmentation agents in treatment-resistant depression [25]. All patients treated in the study began taking the atypical antipsychotic agent after being treated with a variety of established antidepressant medications (including SSRIs, buproprion, venlafaxine, tricyclic antidepressants, mirtazapine, etc.) for at least six weeks. Augmentation with the atypical antipsychotic agents, as a class, produced an impressive overall response rate of >65%. Olanzapine and risperidone in particular demonstrated robust overall response rates (57% and 50%, respectively), whereas quetiapine and ziprasidone had lower response rates (33% and 10%, respectively). As was true of the open-label and double-blind studies, relatively low doses of the atypical antipsychotic agents were employed. Sedation was the most commonly cited reason for discontinuation with quetiapine and ziprasidone, whereas weight gain was the most commonly cited reason for discontinuation with olanzapine.

Obsessive–compulsive disorder

OCD affects 2–3% of the population worldwide. Symptoms of OCD include intrusive and recurrent thoughts, impulses or images that cause marked anxiety and repetitive behaviors (e.g. hand washing, ordering or checking) or mental acts (e.g. praying, counting or repeating words silently) that the person feels driven to perform in response to an obsession. Pharmacotherapy (usually SSRIs) and cognitive–behavioral therapy are useful in treating this disorder. However, only 40–60% of patients with OCD will have a significant reduction in symptoms with current clinical interventions [26]. For patients with an inadequate response to an SSRI, treatment options include switching to other medications, augmentation with other pharmacological agents and, in extreme cases, neurosurgery [26]. As with the treatment of depression, successful augmentation of antidepressant medications with atypical antipsychotic agents has been reported.

Risperidone. Early reports of the effectiveness of augmentation of SSRIs with risperidone in treating refractory OCD included a case series of four pediatric OCD patients and an open-label study of 20 refractory OCD outpatients [27,28]. A double-blind placebo-controlled study of SSRI-refractory OCD patients reported that 50% of the patients responded to augmentation with a low dose (mean daily dose 2.2 mg) of risperidone [29]. Later, two double-blind placebo-controlled studies confirmed the effectiveness of low-dose risperidone augmentation in SSRI-resistant OCD patients [30,31].

Olanzapine. There are multiple open-label reports supporting the effectiveness of olanzapine augmentation of SSRI-refractory OCD [32–34]. However, conflicting results were observed in two double-blind placebo-controlled studies with olanzapine. One study reported no additional advantage of adding olanzapine for six weeks in fluoxetine-refractory OCD patients compared with extending monotherapy [35], whereas another study reported a significant improvement in OCD symptoms with augmentation of olanzapine in SSRI-refractory OCD patients [36]. Both trials had relatively small sample sizes but the positive study had used a higher mean dose of olanzapine (11.2 mg) than had the negative study (6.1 mg). Additional studies seem warranted to address these discrepant findings.

Quetiapine. Promising results of augmentation with quetiapine in SSRI-resistant OCD patients were seen in several open trials [37,38]. However, two other open-label trials showed a lack of efficacy of quetiapine augmentation [39,40]. In addition, one double-blind, placebo-controlled trial showed that the addition of quetiapine is beneficial for patients with SSRI-refractory OCD [41], whereas another double-blind placebo-controlled study reported that quetiapine augmentation was no more effective than placebo augmentation of SSRIs in treatment refractory OCD [42].

Post-traumatic stress disorder

PTSD is an anxiety disorder that can develop after direct exposure to an extreme traumatic event. Symptoms include flashbacks (vivid, disturbing memories of the event), sleep disturbances, guilt, paranoia and panic attacks. The disorder is sometimes associated with combat veterans or victims of violent crimes. PTSD patients can respond to treatment with SSRIs, but response rates are typically below 60% [43]. Improvement in a broad range of symptoms with adjunctive risperidone treatment of PTSD was seen in two double-blind, placebo-controlled studies [44,45]. In these two studies, patients were typically receiving several psychotropic medications, but 79–88% were receiving antidepressants, including SSRIs. SSRI-resistant PTSD was specifically examined in a small double-blind, placebo-controlled trial [46]. In this study, augmentation of olanzapine was associated with significant reductions in PTSD symptoms, especially sleep symptoms.

Generalized anxiety disorder and panic disorder

In addition to PTSD, two other types of anxiety disorders, GAD and PD, were recently shown to be responsive to augmentation with olanzapine. PD is a chronic illness characterized by recurrent, severe, unexplained discreet anxiety attacks (usually with autonomic activation) that have a definite onset and spontaneous termination. GAD is also a chronic illness characterized by excessive anxiety (often excessive worrying), often accompanied by motor tension and hypervigilance. A double-blind placebo-controlled study of augmentation of fluoxetine therapy by olanzapine in refractory GAD patients resulted in a greater proportion of treatment responders [47]. An open-label study of low-dose olanzapine in SSRI-resistant PD patients resulted in 82% of patients responding, with 58% achieving remission [48].

Potential mechanism(s) of action

The clinical data show that atypical antipsychotic agents can be very useful for augmenting responses in patients with poor responses to antidepressant (especially SSRI) treatment. Identifying a potential mechanism of action for this augmentation is complicated by the preliminary nature of some of the reports and the potential differential responses in different diseases. Indeed, different atypical antipsychotic agents might have different mechanisms of action as augmentation agents in different diseases.

One possible mechanism for the augmentation is a pharmacokinetic interaction. Important routes of metabolism for the atypical antipsychotic agents include cytochrome P 2D6 (CYP2D6) for risperidone, CYP1A2 and CYP2D6 for olanzapine, CYP3A4 for quetiapine and ziprasidone, and CYP3A4 and 2D6 for aripiprazole [49,50]. Because several SSRIs inhibit CYP2D6, there is a potential for CYP450 drug–drug interactions. Indeed, a pharmacokinetic interaction between risperidone and fluoxetine has been reported, resulting in a reduced clearance of risperidone [51]. However, coadministration of a relatively high dose of fluoxetine (60 mg) only slightly elevated peak plasma concentrations (by ~18%) and only slightly decreased clearance (by ~15%) of olanzapine [52]. Further, combination therapy with quetiapine and fluoxetine or quetiapine and imipramine had a minimal effect on quetiapine pharmacokinetics and was well tolerated [53]. In addition, the patients treated with augmentation agents are typically treatment resistant and, by definition, unresponsive to any dose of antidepressant. Furthermore, safety data for the combinations are generally similar to those of the component monotherapies. Thus, a pharmacokinetic interaction is unlikely fully to explain the clinical findings.

A more likely explanation for the efficacy of atypical antipsychotic agents as augmentation agents is a pharmacodynamic one. In this regard, there are multiple possible mechanisms of action because the atypical antipsychotic agents have a very rich pharmacology. Indeed, most of the compounds have affinities for multiple dopamine, 5-hydroxytryptamine (5-HT), noradrenaline and histamine receptor subtypes (Table 2). Despite this complexity, do the clinical data offer any clues as to which receptors are the most important?

Dopamine receptors

An obvious suspect is the dopamine D_2 receptor because it has long been accepted to have an important role in the therapeutic effects of antipsychotic drugs. Originally, clinical observations indicated that typical antipsychotic agents (e.g. haloperidol) can, paradoxically, induce depressive symptoms, and concepts such as 'akinetic depression' were introduced [54]. Although the 'depressogenic' effect of typical antipsychotic agents might be related to the induction of EPS [55], it is possible that depressive symptoms might be caused by typical antipsychotic agents in a subgroup of schizophrenic patients [56]. However, recent studies indicate that atypical antipsychotic agents can show efficacy in treating the depressive symptoms of schizophrenia independently of any antipsychotic effects [57–59]. In addition, the antipsychotic agent amisulpride is a relatively selective D_2 and D_3 receptor antagonist and has been reported to be effective in treating dysthymia [60]. An open-label trial with amisulpride suggested that it has beneficial effects as an augmentation strategy in treatment-resistant OCD [61]. One important common feature of the augmentation of SSRI therapy with atypical antipsychotic agents is the low dose employed. In most studies of augmentation of antidepressant therapy, the doses of atypical antipsychotic agents are at the very low end of the usual antipsychotic dose range. The same is true for amisulpride monotherapy for dysthymia (e.g. 50 mg for dysthymia versus 200–400 mg for schizophrenia) [60]. Neuroimaging studies in humans indicate that these low doses of the atypical antipsychotic agents occupy ~50% of D_2 receptors in the striatum [62–69]. Similar studies have shown that 60–70% D_2 occupancy is usually needed for antipsychotic efficacy, whereas greater than 80% D_2 occupancy can produce EPS [70,71]. Thus, a low level of D_2 occupancy might be all that is required for augmentation of antidepressant therapy. Solvay Pharmaceuticals has recently introduced compounds (SLV 310 and SLV314) that have a high affinity for both D_2 receptors and the 5-HT transporter [72,73]. Unfortunately, although these compounds might be beneficial for treating

TABLE 2

Affinity (K_i, nM) of atypical antipsychotic agents for key human recombinant receptor subtypes[a]

	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
D_2	7	11	245	10	1
D_3	14	44	340	10	10
D_4	16	57	1600	39	510
5-HT_{1A}	428	957	432	76	6
5-HT_{2A}	0.2	7	101	0.3	9
5-HT_{2C}	35	70	2502	13	22
5-HT_6	1188	11	1865	61	783
5-HT_7	7	389	308	7	10
H_1	15	4	11	43	30
α_{1A}	5	183	22	18	26
α_{2C}	1	330	29	59	37
M_3	10000	255	10000	10000	4677

[a] Data from Refs [76,77,79].

schizophrenia, their high affinity for the D_2 receptor might preclude their utility as antidepressants. Partial agonism of the D_2 receptor might be clinically equivalent to weak antagonism. Aripiprazole is a partial agonist at D_2 receptors [74]. Unfortunately, at this time, aripiprazole is the least well studied augmenting agent. Additional studies with aripiprazole will help to determine if partial agonism of the D_2 receptor offers any advantages in this patient population. In addition, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole and amisulpride all have affinity for dopamine D_3 receptors, whereas olanzapine, risperidone and ziprasidone also have affinity for dopamine D_4 receptors [75–79]. However, because the respective affinities of these compounds for D_3 and D_4 receptors are lower than their affinities for D_2 receptors, they are likely to occupy much less than 50% of these receptors at the doses employed. Thus, activity at D_3 or D_4 receptors might not have an important role in the augmentation of antidepressant therapy. However, it could also be argued that 50% D_2 occupancy might be too low for any functional significance, and that higher receptor occupancy of other receptors at these low doses (e.g. 5-HT_{2A} receptors; see below) might be the real reason for the antidepressant augmentation effects of atypical antipsychotic drugs.

Serotonin receptors

Antagonist activity at 5-HT_{2A} receptors has been hypothesized to have an important role in making atypical antipsychotic agents atypical [80–82]. Indeed, olanzapine, risperidone, quetiapine and ziprasidone all have higher affinity for 5-HT_{2A} receptors than for D_2 receptors [76–79]. Thus, one would expect higher occupancy of 5-HT_{2A} receptors than of D_2 receptors at the doses given in augmentation studies. Indeed, at the doses used in augmentation trials, olanzapine and risperidone have been shown to occupy >85% of 5-HT_{2A} sites [68]. Further, the antidepressants mirtazapine, mianserin and nefazodone, in addition to affinity for α-adrenoceptors, have high affinity for the 5-HT_{2A} receptor and have also been used successfully as augmentation agents in SSRI nonresponders [83–85]. In support of the role for 5-HT_{2A} receptors, one study reported that a selective 5-HT_{2A} antagonist enhanced the antidepressant-like effects of fluoxetine in a preclinical model of antidepressant activity [86]. Thus, antagonist activity at 5-HT_{2A} receptors is likely to have an important role in the augmentation effects of atypical antipsychotic agents.

The atypical antipsychotic agents also have affinity for other 5-HT receptor subtypes. Albeit lower than their affinity for 5-HT_{2A} receptors, aripiprazole, olanzapine, risperidone and ziprasidone all have high affinity for the closely related 5-HT_{2C} receptor [76–79]. Interestingly, quetiapine does not have appreciable affinity for the 5-HT_{2C} receptor. In addition, aripiprazole, risperidone and ziprasidone all have high affinity for the 5-HT_7 receptor, whereas olanzapine does not. Conversely, olanzapine has high affinity for the 5-HT_6 receptor, whereas aripiprazole, risperidone, quetiapine and ziprasidone do not [76–79]. Thus, antagonism of 5-HT_{2C}, 5-HT_6 or 5-HT_7 receptors might be useful, but does not seem to be necessary, for activity as an augmentation agent. Ziprasidone, aripiprazole and quetiapine also have affinity for the 5-HT_{1A} receptor; however, they might function as partial agonists at this receptor [87,88]. Because at least one clinical study suggests that olanzapine and risperidone are superior to quetiapine and ziprasidone for augmentation of SSRI therapy in MDD [25], activity at 5-HT_{1A} receptors might actually limit the utility of a compound as an augmentation agent in depression.

Other receptors

To varying degrees, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone all have affinity for the histamine H_1 receptor [76–79]. Olanzapine has the highest affinity for H_1 receptors of the group, and the affinity for the H_1 receptor for both olanzapine and quetiapine exceed their affinity for the D_2 receptor. Although it is possible that antagonist activity at the H_1 receptor might have a role in the efficacy of atypical antipsychotic drugs, it has also been hypothesized to have a role in the weight gain seen following treatment with these agents [76]. Indeed, weight gain has been reported in patients being treated with atypical antipsychotic augmentation [25]. H_1 receptor antagonism will also produce sedation and cognitive impairment [89]. Thus, H_1 receptor antagonism is probably an undesirable component of atypical antipsychotic augmentation therapy.

Risperidone, quetiapine, ziprasidone and aripiprazole all also have high affinity for α_1- and α_2-adrenoceptor subtypes [76–79]. However, olanzapine has relatively low affinity for the α-adrenoceptor. Thus, antagonist activity at α_1- and/or α_2-adrenoceptors might have a role in the augmentation effects of all of the atypical antipsychotic agents, except for olanzapine. Quetiapine has a much higher affinity for α-adrenoceptors compared with D_2 receptors. Thus, future clinical studies with quetiapine as an augmentation agent for antidepressants will help to determine the role of α-adrenoceptor antagonism in this augmentation process. Of the atypical antipsychotic agents, only olanzapine and clozapine have affinity for muscarinic acetylcholine receptor subtypes [76–79]. Thus, it seems unlikely that affinity for muscarinic acetylcholine receptors has a major role in the augmentation of antidepressant therapy with atypical antipsychotic agents.

Common functional activity

Given that their binding profiles are overlapping but not identical, it is possible that different antipsychotic agents augment the clinical response of antidepressants via different mechanisms. Thus, the augmentation of antidepressants might have less to do with common antagonism of specific receptors and more to do with a common 'downstream' functional impact on brain systems. For example, common effects on neurotransmitter levels in the prefrontal cortex, even if achieved by different receptor interactions, might underlie the augmentation of atypical antipsychotic agents. In this regard, synergistic effects of multiple antipsychotic agents and SSRIs have been seen on noradrenaline and dopamine levels in the prefrontal cortex of animals; α_2-adrenoceptor antagonism, 5-HT_{2C} receptor antagonism and 5-HT_{1A} receptor agonism can all contribute to this effect [90–92]. In addition, functional interactions on the activity of noradrenaline-containing locus coeruleus neurons, potentially involving at least 5-HT_{2A} antagonism, might have a role in the effects of combined treatment with atypical antipsychotic agents and antidepressants [93–96]. Another potential common functional output for this augmentation effect is neurogenesis because both antidepressants and atypical antipsychotic agents have been shown to enhance neurogenesis [97,98]. However, combined treatment with fluoxetine and olanzapine does not have a

synergistic effect on neurogenesis [99]. Testing of additional combinations is needed to determine if a synergistic effect on neurogenesis has a role in the combined administration of other antidepressants and antipsychotic agents.

Conclusion

Despite efforts to modernize the process of identifying novel drug targets (e.g. transgenic animals and gene chips), sometimes the most important information still comes from serendipitous clinical observation. Thus, even today, drug discovery the 'old-fashioned way' (i.e. working backwards from the clinic to the bench) can still be fruitful. In this regard, recent clinical data indicate that augmentation with low doses of atypical antipsychotic agents can help many patients who have a less than optimal response to antidepressant medication. Although the benefits of using atypical antipsychotic agents in conjunction with antidepressants must be balanced against any potential adverse events (e.g. weight gain, sedation), many patients, suffering from a range of psychiatric disorders, have benefited from this combination therapy. Even though the dataset is clearly incomplete, examination of these clinical findings shows some trends beginning to emerge: olanzapine and risperidone might offer the best outcomes for augmentation in depression, whereas risperidone might offer the best outcome for augmentation in OCD. The mechanism(s) that have the most important role in this augmentation are also not completely clear, and it is possible that different antipsychotic agents have different mechanisms in the different disease states. However, to date, the data indicate that the mechanism almost certainly involves 5-HT_{2A} antagonism, probably involves moderate D_2 antagonism (and perhaps partial agonism), with H_1 antagonism probably contributing to adverse events. Whether activity at other receptor subtypes is useful (e.g. 5-HT_6, 5-HT_7, α-adrenoceptor, muscarinic acetylcholine) is unclear. Additional double-blind, placebo-controlled clinical trials are needed to clarify the exact benefit of the various atypical antipsychotic agents in various psychiatric disorders. Further, preclinical studies examining the effects of a combination of SSRIs and various compounds selective for different receptor subtypes are also needed. Hopefully, these additional studies will lead to improved medications to help the millions of patients suffering from OCD, PTSD, GAD and depression.

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