

# Synergistic Action of 5-HT<sub>2A</sub> Antagonists and Selective Serotonin Reuptake Inhibitors in Neuropsychiatric Disorders

Gerard J Marek<sup>\*1</sup>, Linda L Carpenter<sup>2</sup>, Christopher J McDougle<sup>3</sup> and Lawrence H Price<sup>2</sup>

<sup>1</sup>Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; <sup>2</sup>Department of Psychiatry and Human, Brown Medical School, Mood Disorders Program, Behavior, Butler Hospital, Providence, RI, USA; <sup>3</sup>Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA

Recently, the addition of drugs with prominent 5-HT<sub>2</sub> receptor antagonist properties (risperidone, olanzapine, mirtazapine, and mianserin) to selective serotonin reuptake inhibitors (SSRIs) has been shown to enhance therapeutic responses in patients with major depression and treatment-refractory obsessive–compulsive disorder (OCD). These 5-HT<sub>2</sub> antagonists may also be effective in ameliorating some symptoms associated with autism and other pervasive developmental disorders (PDDs). At the doses used, these drugs would be expected to saturate 5-HT<sub>2A</sub> receptors. These findings suggest that the simultaneous blockade of 5-HT<sub>2A</sub> receptors and activation of an unknown constellation of other 5-HT receptors indirectly as a result of 5-HT uptake inhibition might have greater therapeutic efficacy than either action alone. Animal studies have suggested that activation of 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors may counteract the effects of activating 5-HT<sub>2A</sub> receptors. Additional 5-HT receptors, such as the 5-HT<sub>1B/1D/5/7</sub> receptors, may similarly counteract the effects of 5-HT<sub>2A</sub> receptor activation. These clinical and preclinical observations suggest that the combination of highly selective 5-HT<sub>2A</sub> antagonists and SSRIs, as well as strategies to combine high-potency 5-HT<sub>2A</sub> receptor and 5-HT transporter blockade in a single compound, offer the potential for therapeutic advances in a number of neuropsychiatric disorders.

*Neuropsychopharmacology* (2003) **28**, 402–412. doi:10.1038/sj.npp.1300057

**Keywords:** risperidone; mirtazapine; olanzapine; 5-HT<sub>2A</sub> receptors; depression; obsessive–compulsive disorder

## INTRODUCTION

Blockade of the serotonin (5-hydroxytryptamine; 5-HT) transporter is the common pharmacological action shared by selective serotonin reuptake inhibitors (SSRIs; eg fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram). Enhancement of the synaptic availability of 5-HT appears to be a critical component of the mechanism underlying the action of SSRIs in the treatment of depression, as demonstrated by the tryptophan depletion paradigm (Delgado *et al*, 1990, 1999). While long-term adaptations to blockade of monoamine reuptake must be present to explain the delay in antidepressant efficacy (Duman *et al*, 1997), the relatively rapid (<7 h) return of depressive symptoms in recently remitted patients during the monoamine depletion studies suggests that the long-term adaptations, like enhanced synaptic availability of monoamines, are necessary, but not sufficient, for a

therapeutic response. Both enhanced synaptic availability of monoamines and long-term adaptations appear to be necessary for the therapeutic effect in most depressed patients during the initial month(s) of treatment. However, there are little clinical data regarding which of the known 15 5-HT receptors are involved in mediating the actions of SSRIs in the diverse range of neuropsychiatric syndromes in which they have shown efficacy (eg major depression, obsessive–compulsive disorder (OCD), pervasive developmental disorders (PDDs) such as autism, panic disorder, and post-traumatic stress disorder (PTSD)).

Recently, addition of the 5-HT<sub>2A</sub>/dopamine D<sub>2</sub> receptor antagonist risperidone at low doses to ongoing SSRI treatment has been shown in an open-label study to enhance therapeutic responses in patients with major depression (Ostroff and Nelson, 1999). Patients with treatment-refractory OCD have been shown to benefit from a similar strategy in a double-blind placebo-controlled study (McDougle *et al*, 2000). It is not known whether monotherapy with low-dose risperidone might also possess therapeutic effects in these disorders. Like the SSRIs, risperidone has demonstrated some efficacy as a monotherapy in the treatment of PDDs (McDougle *et al*, 1998; Research Units on Pediatric Psychopharmacology Autism Network, 2002).

\*Correspondence: GJ Marek, Groton Laboratories, Pfizer Inc., Eastern Point Road, MS 8260-2604, Groton, CT 06340, USA, Tel: +1 860 686 1838, Fax: +1 860 686 1839,

E-mail: gerard\_j\_marek@groton.pfizer.com

Received 22 March 2002; revised 31 July 2002; accepted 5 August 2002

Online publication: 13 September 2002 at <http://www.acnp.org/citations/Npp091302378>

The only receptor subtype that risperidone is likely or known to saturate at these lower doses (0.5–1 mg/day) is the 5-HT<sub>2A</sub> receptor (Schotte *et al*, 1996; Nyberg *et al*, 1999; Talvik-Lofti *et al*, 2000). Such findings suggest the hypothesis discussed in detail below, that activation of 5-HT<sub>2A</sub> receptors secondary to the blockade of 5-HT transporters by SSRIs functionally *opposes* the therapeutic effects that are achieved by the activation of non-5-HT<sub>2A</sub> receptors. This review will discuss preclinical evidence for opposing effects of 5-HT<sub>2A</sub> and non-5-HT<sub>2A</sub> receptors that may contribute to a synergistic clinical action between blockade of 5-HT<sub>2A</sub> receptors and activation of non-5-HT<sub>2A</sub> receptors. Then, evidence for the clinical efficacy of 5-HT<sub>2A</sub> antagonists, both in monotherapy and in combination therapy with SSRIs, will be examined.

### INTERACTIONS BETWEEN 5-HT<sub>2A</sub> AND 5-HT<sub>1A</sub> RECEPTORS

At a cellular level, activation of 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors exerts depolarizing and hyperpolarizing effects, respectively, on cortical pyramidal cells (Araneda and Andrade, 1991; Tanaka and North, 1993; Ashby *et al*, 1994; Aghajanian and Marek, 1997). These interactions have been observed both under *in vitro* conditions and during *in vivo* recordings from the rodent medial prefrontal cortex. Similar interactions have also been observed at a behavioral level. For example, stimulation of 5-HT<sub>1A</sub> receptors suppresses head shakes in rats induced by hallucinogenic drugs, which activate 5-HT<sub>2A</sub> receptors (Arnt and Hyttel, 1989; Schreiber *et al*, 1995). Previous studies have demonstrated that systemic administration of 5-HT<sub>1A</sub> agonists can block head shakes induced by direct infusion of the hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) into the medial prefrontal cortex (Granhoff *et al*, 1992; Willins and Meltzer, 1997).

Evidence for opposing effects of activation of 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors has also been obtained from a behavioral screen for antidepressant drugs, rats performing on a differential reinforcement of low rate 72-s (DRL 72-s) schedule (Marek *et al*, 1989a, b; Marek and Seiden, 1994; Jolly *et al*, 1999). This behavioral screen measures a cardinal feature of prefrontal cortical 'executive function,' that is, withholding inappropriate responses (Fuster, 1997). At an operational level, water-deprived animals in this paradigm must wait at least 72 s following the previous response in order to receive a reinforcer (water) for making a response. The efficacy of 5-HT antagonists in exerting an antidepressant-like response on this screen (increased reinforcement rate, decreased response rate, and a cohesive rightward shift in the inter-response time (IRT) histogram) is related to the selectivity of the antagonists for 5-HT<sub>2A</sub> relative to 5-HT<sub>1A</sub> receptors (Marek *et al*, 1989a; Marek and Seiden, 1994).

Interactions have also been observed between 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors at a behavioral level. Opposing effects exist for 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in modulating hyperlocomotion induced in mice by noncompetitive N-methyl-D-aspartate (NMDA) antagonists (Martin *et al*, 1997). A recent study has found clear evidence supporting opposing effects of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in modulating head shakes in rats (Vickers *et al*, 2001). Activation of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors also leads to

opposing effects on sexual function in rodents (Berendsen *et al*, 1990), in a manner suggesting that activation of 5-HT<sub>2A</sub> receptors could be responsible for the sexual side effects of SSRIs. DRL 72-s behavior also appears to involve reciprocal interactions between 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, since 5-HT<sub>2C</sub> agonists, similar to 5-HT<sub>2A</sub> antagonists, exert antidepressant-like actions in rats performing under this operant paradigm (Marek and Seiden, 1988; Martin *et al*, 1998; Marek *et al*, 2001a). In a similar vein, blockade of 5-HT<sub>2C</sub> receptors may attenuate the antidepressant-like effects observed on the DRL 72-s schedule following administration of drugs that block 5-HT<sub>2A</sub> receptors (Marek and Seiden, 1994).

Opposing interactions may also occur between other 5-HT receptors and the 5-HT<sub>2A</sub> receptor. One prominent effect of activating the 5-HT<sub>2A</sub> receptor in the cortex appears to be the induction of glutamate release from thalamocortical afferents (Marek *et al*, 2001b). This anatomical substrate may be of interest with respect to major neuropsychiatric disorders because the likely source of these thalamocortical afferents for the prefrontal cortex, the intralaminar and midline thalamic nuclei project to other important limbic-related forebrain regions such as the ventral striatum (nucleus accumbens) and the amygdala, as well as the prefrontal cortex (Berendse and Groenewegen, 1990, 1991; Su and Bentivoglio, 1990). 5-HT itself is able to suppress late excitatory postsynaptic potentials (EPSPs) induced by the combination of the 5-HT<sub>2</sub> agonist DOI and electrical stimulation of the white matter (Aghajanian and Marek, 1999). Preliminary experiments have suggested that activation of 5-HT<sub>1-like</sub>, 5-HT<sub>5</sub>, or 5-HT<sub>7</sub> receptors may mediate this effect, which opposes 5-HT<sub>2A</sub> receptor activation (G Marek, unpublished observations).

### RISPERIDONE: PHARMACOLOGICAL PROFILE

The actions of risperidone are considered before those of other 5-HT<sub>2</sub> antagonists because this drug is the most potent and selective (with respect to other 5-HT receptors) 5-HT<sub>2A</sub> antagonist available to clinicians. Blockade of 5-HT<sub>2A</sub> receptors is the most potent action of risperidone as assessed by *in vitro* receptor-binding studies (Schotte *et al*, 1996; Richelson and Souder, 2000). This is hardly surprising given that risperidone was developed using blockade of the behavioral effects of hallucinogenic drugs and potency in binding to 5-HT<sub>2A</sub> receptors as two of the principal drug targets. Risperidone is approximately 20 to 50-fold more potent at binding to the 5-HT<sub>2A</sub> receptor than to the  $\alpha_1$ -adrenergic, dopamine D<sub>2</sub>, histamine H<sub>1</sub>, and  $\alpha_2$ -adrenergic receptors (Table 1). It is one of the most selective compounds clinically available with respect to selectivity at the 5-HT<sub>2A</sub> vs the 5-HT<sub>2C</sub> receptor. The 1000-fold selectivity of risperidone for the 5-HT<sub>2A</sub> vs the 5-HT<sub>1A</sub> receptor may also be relevant to the drug's therapeutic actions in mood disorders, OCD, and PDDs.

The dose of risperidone reported to be effective for depression (0.5–1 mg/day) is in contrast to the doses of 3–6 mg/day used in schizophrenia. Risperidone at 4 mg is thought to produce 70–80% occupancy of striatal dopamine D<sub>2</sub> receptors (Nyberg *et al*, 1999). Higher doses increase the likelihood of extrapyramidal side effects. In contrast, the

**Table 1** *In Vitro* Receptor Potency of Risperidone, Olanzapine, and Mirtazapine ( $K_i$ , nM)

Receptor	Risperidone <sup>a</sup>	Olanzapine <sup>a</sup>	Mirtazapine	Mianserin
5-HT <sub>2A</sub>	0.15	1.48	16.4 <sup>b</sup>	7.0 <sup>c</sup>
$\alpha_1$ -Adrenergic	2.7	44	500 <sup>b</sup>	34 <sup>d</sup>
Dopamine D <sub>2</sub>	3.77	20	10000 <sup>b</sup>	2100 <sup>d</sup>
5-HT <sub>1D</sub>	3.9	150	5000 <sup>e</sup>	372 <sup>f</sup>
Histamine H <sub>1</sub>	5.2	0.087	0.14 <sup>b</sup>	0.40 <sup>d</sup>
$\alpha_2$ -Adrenergic	8.0	280	10 <sup>e</sup>	73 <sup>d</sup>
5-HT <sub>2C</sub>	32	4.1	12.9 <sup>e</sup>	10 <sup>f</sup>
5-HT <sub>1A</sub>	190	610	5000 <sup>e</sup>	1148 <sup>f</sup>
Muscarinic	34,000	36	667 <sup>b</sup>	820 <sup>d</sup>

<sup>a</sup>Richelson and Souder (2000) (human receptors). <sup>b</sup>Richelson (2001) (human receptors). <sup>c</sup>Wander *et al* (1986) (human receptors). <sup>d</sup>Richelson and Nelson (1984) (human receptors). <sup>e</sup>De Boer (1996) (animal receptors). <sup>f</sup>Hoyer *et al* (1990) (animal receptors).

0.5–1 mg dose of risperidone probably saturates the 5-HT<sub>2A</sub> receptors. The previous lower estimates for cortical 5-HT<sub>2A</sub> receptor occupancy using N-methyl-spiperone as the radiotracer are now thought to be an underestimate of the true occupancy (Talvik-Lofti *et al*, 2000). Animal studies using *ex vivo* autoradiographic techniques have supported the increased potency of risperidone for displacement of binding to 5-HT<sub>2A</sub> receptors relative to histamine H<sub>1</sub>, dopamine D<sub>2</sub>,  $\alpha_1$ -adrenergic, and  $\alpha_2$ -adrenergic receptors (Schotte *et al*, 1996). Extrapolation of these results to humans would suggest that only the 5-HT<sub>2A</sub> receptor would show appreciable occupation at risperidone doses of 0.5–1 mg.

### RISPERIDONE: CLINICAL ACTIVITY IN MAJOR DEPRESSION, OCD, AND PDD

Several open-label reports with a total of 12 patients have suggested that addition of low-dose risperidone (0.5–1 mg/day) to ongoing treatment with SSRIs may have clinically significant antidepressant action in patients with major depression (O'Connor and Silver, 1998; Ostroff and Nelson, 1999). The report by Ostroff and Nelson is notable for the rapid (1–2 days) antidepressant effect of risperidone addition in the majority of patients. Another open series of five patients suggested that addition of risperidone (0.5–1.5 mg/day) to the monoamine oxidase inhibitor (MAOI) tranylcypromine resulted in a rapid antidepressant effect in patients lacking a satisfactory response to the MAOI alone (Stoll and Haura, 2000). Our own experience with depressed patients has been that the addition of risperidone to ongoing treatment with SSRIs does rapidly induce a therapeutic response, but that this response is not generally sustained (LL Carpenter, LH Price, unpublished observations). These open-label reports will require confirmation from double-blind placebo-controlled studies with respect to response efficacy, speed of response onset, and maintenance of therapeutic efficacy.

As in the depression literature, a number of open-label case series have suggested that addition of risperidone results in a therapeutic response in patients with OCD who have failed to obtain a satisfactory response to monotherapy with SSRIs after an appropriate duration of treatment

(Jacobsen, 1995; McDougle *et al*, 1995b; Ravizza *et al*, 1996; Saxena *et al*, 1996; Stein *et al*, 1997). Recently, these earlier reports have been confirmed by a double-blind placebo-controlled study in which the addition of risperidone in a mean dose of 2.2 mg/day to ongoing SSRI treatment resulted in clinically significant improvement in refractory OCD patients (McDougle *et al*, 2000). The beneficial effects of risperidone did not appear to be limited to patients with chronic motor tics or schizotypal personality disorder, which had appeared to be the case with typical neuroleptic drugs (McDougle *et al*, 1994). Analyses of drug levels in a subset of patients did not reveal any evidence that risperidone might be enhancing the effects of the SSRIs via a pharmacokinetic, rather than pharmacodynamic, interaction.

In all, 14 anecdotal reports and open-label studies of risperidone in children, adolescents, and adults through 1998 have suggested that this atypical neuroleptic is effective in ameliorating repetitive behavior and aggression towards oneself, others, and property in patients with autism and other PDDs (McDougle *et al*, 1998). A double-blind placebo-controlled study in adults with autism and other PDDs has confirmed these earlier reports (McDougle *et al*, 1998). Monotherapy with risperidone in a mean dose of 2.9 mg/day decreased aggression, anxiety, depression, irritability, and repetitive behaviors, although core symptoms involving aberrant social behavior and language were not affected. While this dose of risperidone approaches doses currently recommended for the treatment of schizophrenia and would result in a significant occupation of dopamine D<sub>2</sub> receptors, it is notable that acute dietary tryptophan depletion (McDougle *et al*, 1996) worsened symptoms in adult patients with autistic disorder. Specifically, an increase in repetitive behavior, depression, and anxiety was observed, without any change in social behavior or language. This and other evidence of the involvement of 5-HT in the pathophysiology of PDDs increases the likelihood that the therapeutic action of risperidone in these disorders might also involve 5-HT. In a recently completed multisite controlled trial, risperidone was significantly better than placebo for reducing self-injury, aggression, and agitation in autistic children and adolescents (Research Units on Pediatric Psychopharmacology Autism Network, 2002). The effect size for risperidone in this study was greater than what has been reported with the D<sub>2</sub> antagonist haloperidol in this patient group.

### OLANZAPINE: PHARMACOLOGICAL PROFILE

Olanzapine has a more complicated profile of G-protein-coupled receptor targets than risperidone. In essence, the 'dirty' pharmacological profile of clozapine served as a template for designing an effective atypical neuroleptic medication free of major adverse effects, such as agranulocytosis and seizures. Olanzapine potently blocks 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and histamine H<sub>1</sub> receptors with a low nanomolar affinity (Table 1). Olanzapine is four-to-ten-fold less potent at dopamine D<sub>2</sub>,  $\alpha_1$ -adrenergic, and muscarinic receptors than at the 5-HT<sub>2A</sub> receptor (Bymaster *et al*, 1996; Schotte *et al*, 1996). This mild selectivity for 5-HT<sub>2A</sub> receptors compared to dopamine D<sub>2</sub> receptors is observed in human

positron emission tomography (PET) neuroimaging studies at low olanzapine doses (eg 5 mg), but is lost at higher doses (20 mg) (Kapur *et al*, 1999). Unlike mirtazapine and mianserin (see below, Table 1), olanzapine is approximately 189-fold less potent at displacing binding to  $\alpha_2$ -adrenergic receptors than to 5-HT<sub>2A</sub> receptors. Olanzapine, similar to the other 5-HT<sub>2</sub> antagonists used to augment SSRIs, is also about 412-fold less potent at displacing binding to 5-HT<sub>1A</sub> vs 5-HT<sub>2A</sub> receptors.

### OLANZAPINE: CLINICAL ACTIVITY IN MAJOR DEPRESSION, OCD, AND PDD

The atypical neuroleptic olanzapine has been found to augment the effects of the SSRI fluoxetine in depressed patients who were refractory to SSRI monotherapy (Shelton *et al*, 2001). The most striking finding from this double-blind, placebo-controlled study was that the greatest degree of improvement in the olanzapine+fluoxetine group occurred within the first week of treatment, while patients were receiving only 5 mg/day of olanzapine. This suggests an acceleration in the onset of action in addition to enhancement of efficacy. Notably, this dose of olanzapine would be expected to saturate about 98% of 5-HT<sub>2A</sub> receptors while saturating only about 55% of dopamine D<sub>2</sub> receptors (Kapur *et al*, 1999).

Several open-label studies have also found that a relatively low dose of olanzapine (5 mg) improves the symptoms of patients with OCD who were refractory to SSRIs (Weiss *et al*, 1999; Bogetto *et al*, 2000). However, all of the patients from Bogetto *et al* and 5/8 positive responders from Weiss *et al* were treated with fluvoxamine, which could have elevated olanzapine levels by interactions with cytochrome P450 microsomal isoenzymes. Thus, pharmacokinetic data and experience with different SSRIs will be necessary to conclude that this effect reflects a pharmacodynamic interaction. Furthermore, the utility of olanzapine as an augmenting strategy in OCD may be compromised by sedation in this patient group (Weiss *et al*, 1999). In contrast to studies of olanzapine in the treatment of depression and OCD, there are no published double-blind studies concerning this drug's efficacy in the treatment of autism and other PDDs. However, an open-label case series described positive responses to olanzapine (7.8 mg/day) in patients with autistic disorder and other PDDs (Potenza *et al*, 1999). In a more recently published study employing a parallel-groups design, 12 children with autistic disorder were randomized to 6 weeks of open-label olanzapine or haloperidol (Malone *et al*, 2001). Mean final dosages were 7.9 mg/day for olanzapine and 1.4 mg/day for haloperidol. Five of six subjects in the olanzapine group and three of six in the haloperidol group were responders.

### MIRTAZAPINE AND MIANSERIN: PHARMACOLOGICAL PROFILE

Unlike risperidone, the most potent pharmacological action of mirtazapine and mianserin is blockade of histamine H<sub>1</sub> receptors, which is thought to play a role in the sedative side effects of these drugs (Table 1). Their second most potent pharmacological action is blockade of the 5-HT<sub>2</sub> family of receptors. Mirtazapine and mianserin appear to block the 5-

HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and  $\alpha_2$ -adrenergic receptors with approximately equal affinity. Both drugs are potent antagonists, although at slightly lower affinities, of 5-HT<sub>3</sub> receptors. Like risperidone, mirtazapine and mianserin are at least 300-fold more selective for blocking 5-HT<sub>2A</sub> vs 5-HT<sub>1A</sub> receptors. Both agents lack appreciable affinity for dopamine D<sub>2</sub> receptors. Blockade of  $\alpha_2$ -adrenergic receptors by mirtazapine has attracted significant interest as a potentially important mechanism of therapeutic action by increasing synaptic concentrations of 5-HT in the hippocampus (De Boer, 1996; Haddjeri *et al*, 1997). Specifically, blockade of  $\alpha_2$ -adrenergic heteroreceptors on serotonergic terminals in the prefrontal cortex is thought to play a role in alterations of hippocampal 5-HT. However, it should be noted that mirtazapine does not increase extracellular 5-HT levels in the prefrontal cortex, whereas norepinephrine and dopamine levels are increased (Millan *et al*, 2000). Furthermore, mianserin does not appear to possess appreciable affinity for the same adrenergic autoreceptor as does mirtazapine (De Boer *et al*, 1996). Hjorth and colleagues (Bengtsson *et al*, 2000) failed to observe increased extracellular 5-HT levels in the prefrontal cortex, the ventral hippocampus, or the dorsal hippocampus in response to either mirtazapine or idazoxan, at doses that did clearly block  $\alpha_2$ -adrenergic responses. Finally, there are no double-blind placebo-controlled studies demonstrating clinical antidepressant action for an  $\alpha_2$ -adrenergic antagonist lacking biologically significant 5-HT<sub>2A</sub> receptor affinity. Evidence reported thus far for the selective  $\alpha_2$ -adrenergic antagonist idazoxan suggests that the suspected beneficial effects of this drug for mood disorders may be mostly restricted to bipolar depression (Osman *et al*, 1989; Potter *et al*, 1994; Grossman *et al*, 1999). Taken together, it is far from clear that the beneficial effects from combining mirtazapine or mianserin with SSRIs in depressed patients (discussed below) is due to  $\alpha_2$ -adrenergic blocking activity of these compounds. Blockade of 5-HT<sub>2</sub> receptors is an alternative hypothesis to explain the clinical reports.

### MIRTAZAPINE AND MIANSERIN: CLINICAL ACTIVITY IN MAJOR DEPRESSION, OCD, AND PDD

Augmentation of SSRIs with 5-HT<sub>2</sub> antagonists lacking appreciable dopamine D<sub>2</sub> blocking properties has been investigated. An initial open-label trial reported significant improvement in nearly half of 20 depressed patients in whom mirtazapine was added to ongoing treatment with SSRIs, venlafaxine, desipramine+SSRI, or desipramine+venlafaxine (Carpenter *et al*, 1999). A follow-up double-blind placebo-controlled study corroborated the earlier open-label trial (Carpenter *et al*, 2002). In the controlled study, 84% of the moderate to severely depressed patients randomized either to placebo or mirtazapine (15–30 mg/day) were on SSRIs for a minimum of 4 weeks but did not have a satisfactory response. Using a 50% decrease in the Hamilton Depression Rating Scale (HDRS) as the primary outcome measure, 64% of the mirtazapine-treated patients were considered responders, compared with only 20% of the placebo-treated patients.

Efficacy in enhancing the action of SSRIs in depressed patients has also been examined for mianserin, a compound

with a similar chemical structure as mirtazapine. Maes *et al* (1999) studied the combination of the SSRI fluoxetine (20 mg/day) with mianserin (30 mg/day) compared to fluoxetine alone in an in-patient setting using a double-blind controlled design. Using a 50% decrease in HDRS ratings as the outcome criterion, they observed a 60% response rate in patients given the fluoxetine+mianserin combination from day 1 compared to a 9% response rate in patients treated with fluoxetine monotherapy. A significant separation between groups was observed as early as the first week. A double-blind placebo-controlled comparison of mianserin (30 mg/day)+fluoxetine (20 mg/day) vs placebo+fluoxetine found a significant advantage for the combined treatment group only when excluding the drop-outs from the first 2 weeks of the 6-week trial (Dam *et al*, 1998).

Mianserin may also enhance the efficacy of SSRIs in refractory patients as well. A double-blind, placebo-controlled study comparing addition of mianserin (60 mg/day) or placebo to fluoxetine (20 mg/day) or placebo in patients with  $\geq 25$  score on the 17-item Hamilton Depression Rating (Ham-D) Score observed a significant 5-point advantage for the mianserin+fluoxetine group compared to the placebo+fluoxetine group. The mianserin+placebo group was intermediate between the other two groups. The remission rate was also over twice as great in the mianserin+fluoxetine group vs the placebo+fluoxetine group (Ferreri *et al*, 2001). A recent double-blind study (mianserin+sertraline vs placebo+sertraline) failed to observe beneficial effects of adding mianserin (30 mg/day) to sertraline (100 mg/day) in patients failing to respond to an initial open 6-week treatment with sertraline (50 mg/day  $\times$  4 weeks; 100 mg/day  $\times$  2 weeks; Licht and Qvitzau, 2002). Differences in depression severity may have contributed to these differences. The 17-item HAM-D scores required for study entry was  $\geq 25$  for the fluoxetine augmentation study *after* initial fluoxetine treatment (Ferreri *et al*, 2001), whereas the entry criterion was  $\geq 18$  for the sertraline augmentation study *before* the initial sertraline treatment (Licht and Qvitzau, 2002).

Literature regarding the efficacy of mirtazapine in OCD is limited to a single open-label trial. Only two of 10 patients (or 2/6 completers) improved during a 10-week course of treatment with mirtazapine (Koran *et al*, 2001). Four patients in the study had not had a previous unsuccessful trial with SSRIs, and both of the patients who improved were in this subgroup. To date, there have been no published studies in which mirtazapine was used to augment SSRI monotherapy in treatment-refractory OCD.

A recent open-label study of mirtazapine (mean dose, 32 mg/day) in children, adolescents, and young adults with PDDs (aged 4–24 years) found a 35% response rate in 26 patients, similar to the response rate generally observed in this population with SSRIs (Posey *et al*, 2001). This was a naturalistic study in which the nine mirtazapine responders were on either no concomitant medications (four patients); methylphenidate (two patients); clonidine and pimozone (one patient); paroxetine and risperidone (one patient); or clonazepam and guanfacine (one patient). As with risperidone (see above), clinical improvement was noted for aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia, with no improvement in core symptoms of socialization or communication impairment.

Confirmation of these preliminary results under double-blind placebo-controlled conditions would support the hypothesis that blockade of 5-HT<sub>2A</sub> receptors plays an important role in the therapeutic effects of risperidone for autistic patients. The efficacy of 5-HT<sub>2</sub> antagonists in combination with SSRIs for the treatment of PDDs remains to be explored.

#### OTHER 5-HT<sub>2</sub> ANTAGONISTS: SPECTRUM OF CLINICAL ACTIVITY

While SSRIs have become the mainstay for the pharmacological treatment of major depression, a number of drugs are effective in monotherapy minus the ability to appreciably block either monoamine uptake or monoamine oxidase. These 'atypical' drugs (mirtazapine, mianserin, nefazodone, and trazodone) have been shown to have antidepressant efficacy in multiple double-blind, placebo-controlled studies (Pinder and Fink, 1982; Marek *et al*, 1992; Davis *et al*, 1997; Fawcett and Barkin, 1998). The common potent pharmacological target for these agents is blockade of the 5-HT<sub>2</sub> family of receptors. Interestingly, there have been no controlled studies published suggesting that nefazodone or trazodone might enhance in a synergistic fashion the therapeutic effects of SSRIs. If the 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors are important targets that SSRIs indirectly activate via blockade of the 5-HT transporter, then the lack of selectivity of nefazodone and trazodone at the 5-HT<sub>1A</sub> or the 5-HT<sub>2C</sub> vs the 5-HT<sub>2A</sub> receptors may limit the usefulness of these drugs as augmenting agents for patients refractory to SSRIs (Wander *et al*, 1986; Eison *et al*, 1990; Richelson, 2001). In addition to the well-known 'atypical' antidepressants listed above, there are double-blind studies demonstrating antidepressant activity of other potent 5-HT<sub>2</sub> antagonists as well, such as ritanserin, pipamperone, pizotifen, danitracen, and etoperidone (Matussek *et al*, 1976; Ansoms *et al*, 1977; Standal, 1977; Kern and Richter, 1985; Bersani *et al*, 1990).

In contrast to the preliminary evidence that blockade of 5-HT<sub>2</sub> receptors may augment the therapeutic effects of SSRIs in OCD, evidence from monotherapy with potent 5-HT<sub>2</sub> antagonists in this disorder is generally negative. For example, the atypical neuroleptic clozapine, at doses (400–500 mg/day) that would provide significant blockade of 5-HT<sub>2A</sub> receptors (Nordstrom *et al*, 1993), did not improve any of 10 treatment-refractory patients participating in a 10-week open-label trial (McDougle *et al*, 1995a). Clinical experience with other available 5-HT<sub>2</sub> antagonists in the treatment of OCD has been similarly unrewarding.

In contrast to the apparent benefit of atypical neuroleptic drugs for SSRI-refractory patients with OCD, a number of case reports (generally involving schizophrenic patients) have suggested that addition of atypical neuroleptic drugs can worsen obsessive-compulsive symptoms while simultaneously improving psychotic symptoms (Lykouras *et al*, 2000; Khullar *et al*, 2001; De Haan *et al*, 2002). The magnitude of this clinical problem remains to be fully explored as clozapine may be implicated more frequently than other antipsychotic drugs (De Haan *et al*, 1999). Obsessive-compulsive symptoms have been reported to be improved in schizophrenic patients treated with olanzapine (Poyurovsky *et al*, 2000). Addressing both the issue of

clozapine and the primary psychiatric diagnosis, the open-label trial of clozapine in treatment-refractory OCD patients failed to observe worsening of obsessive-compulsive symptoms for any of the 10 patients treated for 10 weeks (McDougle *et al*, 1995a). The frequency for which exacerbation of obsessive-compulsive symptoms is observed in schizophrenic patients remains to be quantified. Thus, primary OCD *vs* obsessive-compulsive symptoms in patients with other diagnoses may be an important factor in whether addition of 5-HT<sub>2A</sub> antagonists improves patients' refractory to SSRI treatment.

The improvement of aggression in autism by both risperidone and mirtazapine is suggestive that blockade of 5-HT<sub>2A</sub> receptors may play a role in this response. This is interesting in light of a double-blind placebo-controlled crossover trial in which the selective 5-HT<sub>2A</sub> antagonist pipamperone decreased episodes of anger, aggressiveness, and impulsivity, and increased alertness and responsiveness in adult females with mental retardation (van Hemert, 1975). While this report did not specify the clinical diagnoses of the patients, PDDs are known to be over-represented in the population of mentally retarded individuals with prominent behavioral disturbances. This efficacy in treating aggression is consistent with previous open-label trials of pipamperone in diverse groups of patients (DeBerdt, 1976; Van Renynghede de Voxvrie and De Bie, 1976; Noordhuizen, 1977; Haegeman and Duyck, 1978). Pipamperone has since been shown to have significant *in vitro* selectivity as an antagonist at the 5-HT<sub>2A</sub> receptor compared to other receptors (dopamine D<sub>2</sub>, 20-fold; dopamine D<sub>3</sub>, 46-fold; 5-HT<sub>1A</sub>, 512-fold; 5-HT<sub>1D</sub>, 30-fold; 5-HT<sub>2C</sub>, 100-fold; histamine H<sub>1</sub>, 444-fold;  $\alpha_{2A}$ -adrenergic, 159-fold;  $\alpha_{2B}$ -adrenergic, 6.5-fold;  $\alpha_{2C}$ -adrenergic, 54-fold) (Schotte *et al*, 1996).

#### THERAPEUTIC EFFICACY OF SSRIS: WHICH 5-HT RECEPTORS ARE ACTIVATED?

The central thesis argued above is that 5-HT<sub>2A</sub> receptors actually oppose the therapeutic effects of activating non-5-HT<sub>2A</sub> receptors in diverse neuropsychiatric syndromes such as depression, OCD, and PDDs. This broad range of clinical effects may be caused by localization of 5-HT<sub>2A</sub> receptors at critical sites in the prefrontal cortex regulating corticostriatal-pallidal-thalamic loops. The target receptor(s) that actually mediate the therapeutic effects of increased synaptic 5-HT caused by SSRIs is far from clear and may be different for these and other psychiatric syndromes.

5-HT<sub>1A</sub> receptors may be involved in both the treatment (Pineyro and Blier, 1999) and the pathophysiology of major depression (Arango *et al*, 1995; Stockmeier *et al*, 1998). There have been some positive double-blind placebo-controlled studies with the azapirone class of drugs, such as buspirone and gepirone, which are partial 5-HT<sub>1A</sub> agonists that are not as effective as 5-HT itself in maximally activating postsynaptic 5-HT<sub>1A</sub> receptors (Robinson *et al*, 1990; Jenkins *et al*, 1990). However, these agents are not used as front-line monotherapeutic agents for patients with mood disorders. Furthermore, no positive double-blind placebo-controlled reports of antidepressant activity in depressed patients have been reported for the 5-HT<sub>1A</sub> partial agonists tandospirone and flesinoxan. A large

multicenter, double-blind, placebo-controlled trial for ipsapirone failed to observe a significant antidepressant response, despite a placebo response rate of only 35% (Lapierre *et al*, 1998). Finally, it should be noted that no 5-HT<sub>1A</sub> partial agonists have been approved by the FDA for the treatment of major depression. It is not clear if the relative lack of success with 5-HT<sub>1A</sub> agonists in depression and OCD is caused by the following: (1) lack of compounds with sufficient agonist efficacy for postsynaptic receptors, (2) unfavorable pharmacokinetics of presently available drugs, or (3) inadequate therapeutic benefit from stimulation of 5-HT<sub>1A</sub> receptors alone.

The clinical overlap between migraine headache and major depression also raises the question of whether 5-HT<sub>1B/1D</sub> agonists might be useful in depression. Again, a central problem with 5-HT<sub>1B/1D</sub> receptors, as with 5-HT<sub>1A</sub> receptors, is that optimal clinical action might require blockade of presynaptic autoreceptors on the axon terminals of serotonergic neurons and activation of heteroreceptors on the axon terminals of nonserotonergic neurons. Regarding presynaptic autoreceptor antagonists, the lack of efficacy of the 5-HT<sub>1A</sub> somatodendritic autoreceptor antagonist pindolol in augmenting the effects of SSRIs in SSRI-resistant depression (Perez *et al*, 1999) may simply mean that 5-HT<sub>1B</sub> terminal autoreceptors must also be targeted when attempting to increase serotonergic neurotransmission by blocking the 5-HT<sub>1A</sub> autoreceptors. Moreover, it has been argued that pindolol itself is a suboptimal tool for blocking 5-HT<sub>1A</sub> somatodendritic autoreceptors on serotonergic neurons (Kinney *et al*, 2000). Significant potential remains for potent and selective blockade of somatodendritic (5-HT<sub>1A</sub>) and terminal (5-HT<sub>1B/1D</sub>) autoreceptors on serotonergic neurons as a means to enhance the efficacy of SSRIs.

Activation of 5-HT<sub>2C</sub> receptors appears to cause effects that functionally oppose the effects resulting from activation of 5-HT<sub>2A</sub> receptors (see above). These two receptors are differentially regulated by antidepressants in a manner that could have clinical relevance (Berendsen and Broekkamp, 1991). Other preclinical work in rodents has found that 5-HT<sub>2C</sub> agonists have antidepressant-like action in the forced swim test, the olfactory bulbectomy model, and the DRL 72-s schedule (Martin *et al*, 1998; Cryan and Lucki, 2000). Moreover, a polymorphism for the 5-HT<sub>2C</sub> receptor has been linked to mood disorders (Lerer *et al*, 2001). This might result in an alteration of 5-HT<sub>2C</sub> function independent of receptor abundance. Alterations in RNA editing of 5-HT<sub>2C</sub> receptors has been reported in suicide victims (Niswender *et al*, 2001). Thus, simultaneous blockade of 5-HT<sub>2A</sub> receptors and activation of 5-HT<sub>2C</sub> receptors could result in an improved therapeutic benefit over either of these actions in isolation.

Blockade of 5-HT<sub>2C</sub> receptors could contribute to the enhanced efficacy of augmentation or combination therapy with mirtazapine, mianserin, or olanzapine. If blockade of 5-HT<sub>2C</sub> receptors mediates the antidepressant augmenting effects of 5-HT<sub>2</sub> antagonists, then one might expect an SSRI with potent 5-HT<sub>2C</sub> receptor antagonist potency to have a faster onset of action. Fluoxetine has been suggested from extrapolations of preclinical data to block 5-HT<sub>2C</sub> receptors at doses used in the clinic (Bymaster *et al*, 2002). However, meta-analysis suggests that fluoxetine may have a slower

onset of antidepressant action than other SSRIs (Edwards and Anderson, 1999). It remains to be determined if this is because of pharmacodynamic and/or pharmacokinetic considerations. Alternatively, suggestions that risperidone or pipamperone may augment the action of antidepressant drugs at doses with a measure of selectivity for blockade of 5-HT<sub>2A</sub> receptors might reflect the complex actions of 5-HT in mediating the therapeutic actions of antidepressant drugs (Ostroff and Nelson, 1999; Ansoms *et al*, 1977). In fact, the failure of the pharmaceutical industry to produce an effective antidepressant that selectively activates a single 5-HT receptor is consistent with the likelihood that indirect activation of multiple 5-HT receptor subtypes mediates the therapeutic actions of SSRIs.

The 5-HT<sub>5A/5B</sub> receptor is still poorly understood; indeed, its *in situ* postreceptor transduction pathway is not known. This receptor is most closely related to some of the 5-HT<sub>1</sub> receptor subtypes on a pharmacological basis. Furthermore, *in vitro* studies have demonstrated that the 5-HT<sub>5A</sub> receptor, like the 5-HT<sub>1</sub> family of receptors, can couple to G<sub>i</sub>/G<sub>o</sub> proteins (Francken *et al*, 1998). The 5-HT<sub>5A/5B</sub> receptors are not known to be a target of antidepressant or neuroleptic drugs (Matthes *et al*, 1993). There is presently little data to indicate whether 5-HT<sub>5A/5B</sub> receptors mediate any of the clinical effects of increased synaptic 5-HT subsequent to blockade of 5-HT transporters. Interestingly, a recent report has implicated a polymorphism for this receptor in altered susceptibility to schizophrenia and mood disorders (Birkett *et al*, 2000).

There is some evidence suggesting that activation of 5-HT<sub>6</sub> receptors might oppose the effects of 5-HT<sub>2A</sub> receptor activation in the frontal cortex. Activation of 5-HT<sub>2A</sub> receptors increases glutamate release from thalamocortical afferents, as discussed above. In contrast, blockade of 5-HT<sub>6</sub> receptors has recently been shown to increase extracellular levels of glutamate measured using *in vivo* dialysis in the prefrontal cortex, hippocampus, and striatum (Dawson *et al*, 2000, 2001). Activation of 5-HT<sub>6</sub> receptors might, therefore, be expected to suppress extracellular levels of glutamate in the frontal cortex. Consistent with the hypothesis that functional relationships exist between 5-HT<sub>6</sub> receptors and glutamate, blockade of ionotropic glutamate receptors decreases the expression of 5-HT<sub>6</sub> receptor mRNA (Healy and Meador-Woodruff, 1999).

5-HT<sub>7</sub> agonists might also be in functional opposition to the effects of 5-HT<sub>2A</sub> receptor activation in the prefrontal cortex. For example, high concentrations of 8-OH-DPAT (10 μM) suppressed delayed late EPSPs induced by concurrent activation of 5-HT<sub>2A</sub> receptors and electrical stimulation of the white matter in a delayed manner with only partial efficacy followed by complete recovery (G Marek, unpublished observations). However, effects of 8-OH-DPAT at 5-HT<sub>1A</sub> receptors in slice preparations are usually brisk in onset and only slowly fade away. Thus, these 8-OH-DPAT responses do not appear to be mediated by activation of 5-HT<sub>1A</sub> receptors. This action of 8-OH-DPAT was probably the result of activating a 5-HT<sub>1D/5A/5B/7</sub> receptor. As discussed for the 5-HT<sub>6</sub> receptor, blockade of ionotropic glutamate receptors also alters 5-HT<sub>7</sub> receptor mRNA expression (Healy and Meador-Woodruff, 1999). Further support for the hypothesis that activation of a G<sub>q</sub>-

coupled receptor (positively coupled to adenylyl cyclase) might actually suppress glutamate release induced by 5-HT<sub>2A</sub> receptor activation comes from experiments in which the suppressant action of epinephrine or norepinephrine on DOI-induced late EPSPs is blocked by β<sub>2</sub>-adrenergic antagonists (B Ramos and G Marek, unpublished observations). β<sub>2</sub>-Adrenergic, like 5-HT<sub>4/6/7</sub> receptors are well-known to be coupled to G<sub>q</sub>s proteins. Activation of members of the 5-HT or adrenergic receptor superfamily that increase cAMP formation (eg 5-HT<sub>4/6/7</sub>), with subsequent upregulation of neurotrophins and transcription factors, has also been proposed to play an important role in the long-term effects of antidepressant drugs (Duman *et al*, 1997). Thus, activation of 5-HT<sub>6/7</sub> receptors might have both acute and long-term effects that could contribute to the therapeutic actions of SSRIs.

## CONCLUSIONS AND FUTURE DIRECTIONS

SSRIs have been found to exert clinical efficacy in a wide variety of psychiatric syndromes, including major depression, OCD, autism and other PDDs, panic disorder, and PTSD. Drugs that block the 5-HT<sub>2</sub> family of receptors, such as risperidone, olanzapine, mirtazapine, and mianserin, have been found to either augment the action of SSRIs in treatment-refractory patients or to demonstrate therapeutic efficacy as stand-alone agents. The most parsimonious explanation for these findings is that blockade of 5-HT<sub>2A</sub> receptors and activation of non-5-HT<sub>2A</sub> receptors may have similar effects. Further evidence relevant to this hypothesis will come from the systematic examination of other 'atypical' neuroleptics with respect to their clinical profile of action across diverse psychiatric syndromes. For example, ziprasidone is even more selective for the 5-HT<sub>2A</sub> receptor vs dopamine D<sub>2</sub> or 5-HT<sub>2C</sub> receptors than is risperidone or olanzapine (Schotte *et al*, 1996; Tandon *et al*, 1997). Unlike most other neuroleptics, ziprasidone is a 5-HT<sub>1A</sub> partial agonist (Sprouse *et al*, 1999) that also blocks monoamine transport with sub-μM potency. This drug is relatively weak at displacing binding to histamine H<sub>1</sub> receptors compared to other 'atypical' neuroleptics. A further difference from other 'atypical' compounds is the high potency that ziprasidone possesses for the 5-HT<sub>1D</sub> receptor, and blockade of the 5-HT<sub>1D</sub> autoreceptor enhances the effects of SSRIs on extracellular 5-HT levels (Rollema *et al*, 1996).

Support for the hypothesis that blockade of 5-HT<sub>2A</sub> receptors coincident with activation of non-5-HT<sub>2A</sub> receptors results in more robust clinical activity than either drug alone could come from clinical testing of highly selective 5-HT<sub>2A</sub> antagonists, such as M100907 (Kehne *et al*, 1996), in combination with SSRIs. Evaluation of novel compounds that combine equal and potent blockade of both 5-HT<sub>2A</sub> receptors and 5-HT transporters would also provide critical data (Puller *et al*, 2000; Schmidt *et al*, 2001). An appreciation of the opposing effects of different 5-HT receptor subtypes in mediating the therapeutic effects of drugs will be important in better defining the neurocircuitry involved in the pathogenesis of these disorders, and in developing treatments with more rapid onset and greater efficacy.

## REFERENCES

- Aghajanian GK, Marek GJ (1997). Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. *Neuropharmacology* **36**: 589–599.
- Aghajanian GK, Marek GJ (1999). Serotonin, via 5-HT<sub>2A</sub> receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. *Brain Res* **825**: 161–171.
- Ansoms C, De Backer-Dierick G, Vereecken JLT (1977). Sleep disorders in patients with severe mental depression: double-blind placebo-controlled evaluation of the value of pipamperone (Dipiperon). *Acta Psychiatr Scand* **55**: 116–122.
- Araneda R, Andrade R (1991). 5-Hydroxytryptamine<sub>2</sub> and 5-Hydroxytryptamine<sub>1A</sub> receptors mediate opposing responses on membrane excitability in rat association cortex. *Neuroscience* **40**: 399–412.
- Arango V, Underwood MD, Gubbi AV, Mann JJ (1995). Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res* **688**: 121–133.
- Arnt J, Hyttel J (1989). Facilitation of 8-OHDPAT-induced forepaw treading of rats by the 5-HT<sub>2</sub> agonist DOI. *Eur J Pharmacol* **161**: 45–51.
- Ashby CR, Edwards E, Wang RY (1994). Electrophysiological evidence for a functional interaction between 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in the rat medial prefrontal cortex: an iontophoretic study. *Synapse* **17**: 173–181.
- Bengtsson HJ, Kele J, Johansson J, Hjorth S (2000). Interaction of the antidepressant mirtazapine with  $\alpha_2$ -adrenoceptors modulating the release of 5-HT in different rat brain regions *in vivo*. *Naunyn-Schmiedeberg's Arch Pharmacol* **362**: 406–412.
- Berendse HW, Groenewegen HJ (1990). Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. *J Comp Neurol* **299**: 187–228.
- Berendse HW, Groenewegen HJ (1991). Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. *Neuroscience* **42**: 73–102.
- Berendsen HHG, Broekkamp CLE (1991). Attenuation of 5-HT-1A and 5-HT-2 but not 5-HT-1C receptor mediated behaviour in rats following chronic treatment with 5-HT receptor agonists, antagonists or anti-depressants. *Psychopharmacology* **105**: 219–224.
- Berendsen HHG, Jenck F, Broekkamp CLE (1990). Involvement of 5-HT<sub>1C</sub> receptors in drug induced penile erections in rats. *Psychopharmacology* **101**: 57–61.
- Bersani G, Pozzi F, Marini S, Grispi A, Pasini A, Ciani N (1990). 5-HT<sub>2</sub> receptor antagonism in dysthymic disorder: a double blind placebo-controlled study with ritanserin. *Acta Physiol Scand* **83**: 244–248.
- Birkett JT, Arranz MJ, Munro J, Osbourn S, Kerwin RW, Collier DA (2000). Association analysis of the 5-HT<sub>5A</sub> gene in depression, psychosis and antipsychotic response. *Neuro Report* **11**: 2017–2020.
- Bogetto F, Bellino S, Vaschetto P, Ziero S (2000). Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. *Psychiatry Res* **96**: 91–98.
- Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC et al (1996). Radioceptor binding profile of the atypical antipsychotic olanzapine. *Neuro psychopharmacology* **14**: 87–96.
- Bymaster FP, Zhang W, Carter PA, Shaw J, Chernet E, Phebus L et al (2002). Fluoxetine, but not other selective serotonin uptake inhibitors, increases extracellular norepinephrine and dopamine extracellular levels in prefrontal cortex. *Psychopharmacology* **160**: 353–361.
- Carpenter LL, Jovic Z, Hall JM, Rasmussen SA, Price LH (1999). Mirtazapine augmentation in the treatment of refractory depression. *J Clin Psychiatry* **60**: 45–49.
- Carpenter LL, Yasmin S, Price LH (2002). A double-blind placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* **51**: 183–188.
- Cryan JF, Lucki I (2000). Antidepressant-like behavioral effects mediated by 5-hydroxytryptamine(2C) receptors. *J Pharmacol Exp Ther* **295**: 1120–1126.
- Dam J, Ryde L, Svejso J, Lauge N, Lauritsen B, Bech P (1998). Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiatry* **31**: 48–54.
- Davis R, Whittington R, Bryson HM (1997). Nefazodone: a review of its pharmacology and clinical efficacy in the management of major depression. *Drugs* **53**: 608–636.
- Dawson LA, Nguyen HP, Li P (2000). *In vivo* effects of the 5-HT<sub>6</sub> antagonist SB-271046 on striatal and frontal cortex extracellular concentrations of noradrenaline, dopamine, 5-HT, glutamate and aspartate. *Br J Pharmacol* **130**: 23–26.
- Dawson LA, Nguyen HQ, Li P (2001). The 5-HT<sub>6</sub> receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. *Neuropsychopharmacology* **25**: 662–668.
- De Boer T (1996). The pharmacologic profile of mirtazapine. *J Clin Psychiatry* **57**: 19–25.
- De Boer T, Nefkens F, Van Helvoirt A, Van Delft AML (1996). Differences in modulation of noradrenergic and serotonergic transmission by the alpha-2 adrenoceptor antagonists, mirtazapine, mianserin and idazoxan. *J Pharmacol Exp Ther* **277**: 852–860.
- De Haan L, Linszen DH, Gorsira R (1999). Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disturbances. *J Clin Psychiatry* **60**: 364–365.
- De Haan L, Bevk N, Hoogenboom B, Dingemans P, Linzen D (2002). Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent onset schizophrenia as related disorders. *J Clin Psychiatry* **63**: 104–107.
- DeBerdt R (1976). Pipamperone (Dipiperon) in the treatment of behavioural disorders: a large scale multicentre evaluation. *Acta Psychiatr Belg* **76**: 157–166.
- Delgado PL, Chamey DS, Price LH, Aghajanian GK, Landis H, Heninger GR (1990). Serotonergic function and the mechanism of antidepressant action. Reversal of antidepressant induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry* **47**: 411–418.
- Delgado PL, Miller HL, Salomon RM, Licinio J, Krystal JH, Morens FA et al (1999). Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. *Biol Psychiatry* **46**: 212–220.
- Duman RS, Heninger GR, Nestler EJ (1997). A molecular and cellular theory of depression. *Arch Gen Psychiatry* **54**: 597–606.
- Edwards JG, Anderson I (1999). Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* **57**: 507–533.
- Eison AS, Eison MS, Torrente JR, Wright RN, Yocca FD (1990). Nefazodone: preclinical pharmacology of a new antidepressant. *Psychopharmacol Bull* **26**: 311–315.
- Fawcett J, Barkin RL (1998). Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. *J Affect Disord* **51**: 267–285.
- Ferreri M, Lavergne F, Berlin I, Payan C, Peuch AJ (2001). Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. *Acta Psychiatr Scand* **103**: 66–72.
- Francken JB, Jurzak M, Vanhauwe JFM, Luyten WHML, Leysen JE (1998). The human 5-HT<sub>5A/5B</sub> receptor couples to G<sub>i</sub>/G<sub>o</sub> proteins

- and inhibits adenylate cyclase in HEK 293 cells. *Eur J Pharmacol* **361**: 299–309.
- Fuster JM (1997). *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe*, 3rd edn. Lippincott-Raven: Philadelphia, New York.
- Granhoff MI, Lee L, Jackson A, Patel K, Martinez Y, Ashby CR et al (1992). The interaction of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptors in the medial prefrontal cortex: behavioral studies. *Soc Neurosci Abstr* **18**: 1380.
- Grossman F, Potter WZ, Brown EA, Maislin G (1999). A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. *J Affect Disord* **56**: 237–243.
- Haddjeri N, Blier P, de Montigny C (1997). Effects of long-term treatment with the  $\alpha_2$ -adrenoceptor antagonist mirtazepine on 5-HT neurotransmission. *Naunyn-Schmiedeberg Arch Pharmacol* **355**: 20–29.
- Haegeman J, Duyck E (1978). A retrospective evaluation of pipamperone (Dipiperon) in the treatment of behavioural deviations in severely mentally handicapped. *Acta Psychiatrica Belg* **78**: 393–398.
- Healy DJ, Meador-Woodruff JH (1999). Ionotropic glutamate receptor modulation of 5-HT<sub>6</sub> and 5-HT<sub>7</sub> mRNA expression in rat brain. *Neuropsychopharmacology* **21**: 341–351.
- Hoyer D, Schoeffter P, Waerber C, Palacios JM (1990). Serotonin 5-HT<sub>1D</sub> receptors. *Ann NY Acad Sci* **600**: 168–181.
- Jacobsen FM (1995). Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry* **56**: 423–429.
- Jenkins SW, Robinson DS, Fabre LF, Andary JJ, Messina ME, Reich LA (1990). Gepirone in the treatment of major depression. *J Clin Psychopharmacol* **10**: 77S–85S.
- Jolly DC, Richards JB, Seiden LS (1999). Serotonergic mediation of DRL 72s behavior: receptor subtype involvement in a behavioral screen for antidepressant drugs. *Biol Psychiatry* **45**: 1151–1162.
- Kapur S, Zipursky RB, Remington G (1999). Clinical and theoretical implications of 5-HT<sub>2</sub> and D<sub>2</sub> receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* **156**: 286–293.
- Kehne JH, Baron BM, Carr AA, Chaney SR, Elands J, Feldman DJ et al (1996). Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT<sub>2A</sub> antagonist with a favorable CNS safety profile. *J Pharmacol Exp Ther* **277**: 968–981.
- Kern U, Richter (1985). Clinical comparison of etoperidone and amitriptyline in endogenous depressive patients. *Pharmacopsychiatry* **18**: 94–95.
- Khullar A, Chue P, Tibbo P (2001). Quetiapine and obsessive-compulsive symptoms (OCS): case report and review of atypical antipsychotic-induced OCS. *J Psychiatry Neurosci* **26**: 55–59.
- Kinney GG, Taber MT, Gribkoff VK (2000). The augmentation hypothesis for improvement of antidepressant therapy. *Mol Neurobiol* **21**: 137–152.
- Koran LM, Quirk T, Lorberbaum JP, Elliott M (2001). Mirtazapine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol* **21**: 537–538.
- Lapierre YD, Silverstone P, Reesal RT, Saxena B, Turner P, Bakish D et al (1998). A Canadian multicenter study of three fixed doses of controlled-release ipsapirone in outpatients with moderate to severe major depression. *J Clin Psychopharmacol* **18**: 268–273.
- Lerer B, Macciardi F, Segman RH, Adolfsson R, Blackwood D, Blairy S et al (2001). Variability of 5-HT<sub>2C</sub> receptor cys23ser polymorphism among European populations and vulnerability to affective disorder. *Mol Psychiatry* **6**: 579–585.
- Licht RW, Qvitzau S (2002). Treatment strategies in patients with major depression not responding to first-line sertraline treatment. *Psychopharmacology* **161**: 143–151.
- Lykouras L, Zervas IM, Gournellis R, Malliori M, Rabavilas A (2000). Olanzapine and obsessive-compulsive symptoms. *Eur Neuropsychopharmacol* **10**: 385–387.
- Maes M, Libbrecht I, Van Hunsel F, Campens D, Meltzer HY (1999). Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J Clin Psychopharmacol* **19**: 177–182.
- Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA (2001). Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *J Am Acad Child Adolesc Psychiatry* **40**: 887–894.
- Marek GJ, Li AA, Seiden LS (1989a). Selective 5-hydroxytryptamine<sub>2</sub> antagonists have antidepressant-like effects on differential-reinforcement-of-low-rate 72-second schedule. *J Pharmacol Exp Ther* **250**: 52–59.
- Marek GJ, Li AA, Seiden LS (1989b). Evidence for involvement of 5-hydroxytryptamine<sub>1</sub> receptors in antidepressant-like drug effects on differential-reinforcement-of-low-rate 72-second behavior. *J Pharmacol Exp Ther* **250**: 60–71.
- Marek GJ, Martin-Ruiz R, Abo A, Artigas F (2001a). Synergistic ‘antidepressant-like’ action between a highly selective 5-HT<sub>2A</sub> antagonist (M100907) and the SSRI fluoxetine on DRL 72-s behavior. *Soc Neurosci Abstr* **27**: 975.8.
- Marek GJ, Wright RA, Gewirtz JC, Schoepp DD (2001b). A major role for thalamocortical afferents in serotonergic hallucinogen receptor function in neocortex. *Neuroscience* **105**: 113–126.
- Marek GJ, McDougale CJ, Price LH, Seiden LS (1992). A comparison of trazodone and fluoxetine: implications for a serotonergic mechanism of antidepressant action. *Psychopharmacology* **109**: 2–11.
- Marek GJ, Seiden LS (1988). Effects of selective 5-hydroxytryptamine-2 and nonselective 5-hydroxytryptamine antagonists on the differential-reinforcement-of-low-rate 72-second schedule. *J Pharmacol Exp Ther* **244**: 650–658.
- Marek GJ, Seiden LS (1994). Antidepressant drug screens and the serotonin system. In: Palomo T, Archer T (eds). *Strategies for Studying Brain Disorders: Depressive, Anxiety and Drug Abuse Disorders*. Farrand Press: London. Vol 1, pp 23–40.
- Martin JR, Bos M, Jenck F, Moreau J, Mutel V, Sleight AJ et al (1998). 5-HT<sub>2C</sub> receptor agonists: pharmacological characteristics and therapeutic potential. *J Pharmacol Exp Ther* **286**: 913–924.
- Martin P, Waters N, Carlsson A, Carlsson ML (1997). The apparent antipsychotic action of the 5-HT<sub>2A</sub> receptor antagonist M100907 in a mouse model of schizophrenia is counteracted by ritanserin. *J Neural Transm* **104**: 561–564.
- Matthes H, Boschert U, Amlaiiky N, Grailhe R, Plassat J-L, Muscatelli F et al (1993). Mouse 5-hydroxytryptamine<sub>5A</sub> and 5-hydroxytryptamine<sub>5B</sub> receptors define a new family of serotonin receptors: cloning, functional expression, and chromosomal localization. *Mol Pharmacol* **43**: 313–319.
- Matussek VN, Benkert O, Fidetis K, Flach D, Hermann HU, Kaumeier S et al (1976). Wirkung des Anthracenderivats danitracen (WA 335-BS) im Vergleich zu amitriptylin bei depressiven Patienten. *Arzneim Forsch (Drug Res)* **26**: 1160.
- McDougale CJ, Barr LC, Goodman WK, Pelton GH, Aronson SC, Anand A et al (1995a). Lack of efficacy of clozapine monotherapy in refractory obsessive-compulsive disorder. *Am J Psychiatry* **152**: 1812–1814.
- McDougale CJ, Fleischmann RL, Epperson CN, Wasyluk S, Leckman JF, Price LH (1995b). Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. *J Clin Psychiatry* **56**: 526–528.
- McDougale CJ, Epperson CN, Pelton GH, Wasyluk S, Price LH (2000). A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibition-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* **57**: 794–801.

- McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH (1994). Haloperidol addition to fluvoxamine-refractory obsessive-compulsive disorder: a double-blind, placebo-controlled study in patients with and without tics. *Arch Gen Psychiatry* 51: 302–308.
- McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH (1998). A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders [see comments]. *Arch Gen Psychiatry* 55: 633–641.
- McDougle CJ, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH (1996). Effects of tryptophan depletion in drug-free adults with autistic disorder. *Arch Gen Psychiatry* 53: 993–1000.
- Millan MJ, Gobert A, Rivet JM, Adhumeau-Auclair A, Cussac D, Newman-Tancredi A et al (2000). Mirtazapine enhances fronto-cortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of alpha2-adrenergic and serotonin2C receptors: a comparison with citalopram. *Eur J Neurosci* 12: 1079–1095.
- Niswender CM, Herrick-Davis K, Dilley GE, Meltzer HY, Overholser JC, Stockmeier CA et al (2001). RNA editing of the human serotonin 5-HT<sub>2C</sub> receptor: alterations in suicide and implications for serotonergic pharmacotherapy. *Neuropsychopharmacology* 24: 478–491.
- Noordhuizen GJM (1977). Treating severe maladjustment with pipamperone (Dipiperon). *Acta Psychiatr Belg* 77: 754–760.
- Nordstrom A-L, Farde L, Halldin C (1993). High 5-HT<sub>2</sub> receptor occupancy in clozapine treated patients demonstrated by PET. *Psychopharmacology* 110: 365–367.
- Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L (1999). Suggested minimal effective dose of risperidone based on PET-measured D<sub>2</sub> and 5-HT<sub>2A</sub> receptor occupancy in schizophrenia patients. *Am J Psychiatry* 156: 869–875.
- O'Connor M, Silver H (1998). Adding risperidone to selective serotonin reuptake inhibitor improves chronic depression. *J Clin Psychopharmacol* 18: 89–90.
- Osman OT, Rudorfer MV, Potter WZ (1989). Idazoxan: a selective  $\alpha_2$ -antagonist and effective sustained antidepressant in two bipolar depressed patients. *Arch Gen Psychiatry* 46: 958–959.
- Ostroff RB, Nelson JC (1999). Risperidone augmentation of SSRIs in major depression. *J Clin Psychiatry* 60: 256–259.
- Perez V, Soler J, Puigdemont D, Alvarez E, Artigas F (1999). A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Arch Gen Psychiatry* 56: 375–379.
- Pinder RM, Fink M (1982). Mianserin. *Mod Probl Pharmacopsychiatry* 18: 70–101.
- Pineyro G, Blier P (1999). Autoregulation of serotonin neurons: role in antidepressant drug action. *Pharmacol Rev.* The American Society for Pharmacology and Therapeutics. Vol. 51: 533–591.
- Posey DJ, Guenin KD, Kohn AE, Swiezy NB, McDougle CJ (2001). A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *J Child Adolesc Psychopharmacol* 11: 267–277.
- Potenza MN, Holmes JP, Kaner SJ, McDougle CJ (1999). Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *J Clin Psychopharmacol* 19: 37–44.
- Potter WZ, Grossman F, Dawkins K, Manji HK (1994). Initial clinical psychopharmacological studies of alpha-2 adrenoceptor antagonists in volunteers and depressed patients. In: Montgomery SA, Corn TH (eds). *Psychopharmacology of Depression*, Vol British Association for Psychopharmacology Monograph No. 13. Oxford University Press: New York.
- Poyurovsky M, Dorfman-Etrog P, Hermesh H, Munitz H, Tollefson GD, Weizman A (2000). Beneficial effect of olanzapine in schizophrenic patients with obsessive-compulsive symptoms. *Int Clin Psychopharmacol* 15: 169–173.
- Puller IA, Carney SL, Colvin EM, Lucaites VL, Nelson DL, Wedley S (2000). LY367265, an inhibitor of the 5-hydroxytryptamine transporter and 5-hydroxytryptamine<sub>2A</sub> receptor antagonist: a comparison with the antidepressant, nefazodone. *Eur J Pharmacol* 407: 39–46.
- Ravizza L, Barzegar G, Bellino S, Bogetto F, Maina G (1996). Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). *Psychopharmacol Bull* 32: 677–682.
- Research Units on Pediatric Psychopharmacology Autism Network (2002). A double-blind placebo-controlled trial of risperidone in children with autistic disorder. *N Engl J Medicine* (in press).
- Richelson E (2001). Pharmacology of antidepressants. *Mayo Clin Proceed* 76: 511–527.
- Richelson E, Nelson A (1984). Antagonism by antidepressants of neurotransmitter receptors of normal human brain *in vitro*. *J Pharmacol Exp Ther* 230: 94–102.
- Richelson E, Souder T (2000). Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. *Life Sci* 68: 29–39.
- Robinson DS, Rickels K, Feighner J, Fabre LF, Gammans RE, Shrotriya RC et al (1990). Clinical effects of the 5-HT<sub>1A</sub> partial agonists in depression: a composite analysis of buspirone in the treatment of depression. *J Clin Psychopharmacol* 10: 67S–76S.
- Rollema H, Clarke T, Sprouse JS, Schulz DW (1996). Combined administration of a 5-hydroxytryptamine (5-HT)<sub>1D</sub> antagonist and a 5-HT reuptake inhibitor synergistically increases 5-HT release in guinea pig hypothalamus *in vivo*. *J Neurochem* 67: 437–439.
- Saxena S, Wang D, Bystritsky A, Baxter Jr LR (1996). Risperidone augmentation of SRI treatments for refractory obsessive-compulsive disorder. *J Clin Psychiatry* 57: 303–306.
- Schmidt CJ, Fox CB, Harms JF, Wylie P, Seeger TF, Guanowsky V et al (2001). CP-646,781: a potent dual SSRI/5-HT<sub>2A</sub> receptor agonist. *Soc Neurosci Abstr* 27: 665.17.
- Schotte A, Janssen PFM, Gommeren W, Luyten WHML, Van Gompel P, Lesage AS et al (1996). Risperidone compared with new and reference antipsychotic drugs: *in vitro* and *in vivo* receptor binding. *Psychopharmacology* 124: 57–73.
- Schreiber R, Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ (1995). (1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytryptamine(5-HT)<sub>2A</sub> receptors: modulation by novel 5-HT<sub>2A/2C</sub> antagonists, D<sub>1</sub> antagonists and 5-HT<sub>1A</sub> agonists. *J Pharmacol Exp Ther* 273: 101–112.
- Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG et al (2001). A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 158: 131–134.
- Sprouse JS, Reynolds LS, Braselton JP, Rollema H, Zorn SH (1999). Comparison of the novel antipsychotic ziprasidone with clozapine and olanzapine: inhibition of dorsal raphe cell firing and the role of 5-HT<sub>1A</sub> receptor activation. *Neuropsychopharmacology* 21: 622–631.
- Standal JE (1977). Pizotifen as an antidepressant. *Acta Physiol Scand* 56: 276–279.
- Stein DJ, Bouwer MB, Hawkrigde S, Emsley RA (1997). Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. *J Clin Psychiatry* 58: 119–122.
- Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Fredman L, Raj Kowska G et al (1998). Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression—post-mortem evidence for decreased serotonin activity. *J Neurosci* 18: 7394–7401.

- Stoll AL, Haura G (2000). Tranylcypramine plus risperidone for treatment-refractory major depression. *J Clin Psychopharmacol* **20**: 495–496.
- Su HS, Bentivoglio M (1990). Thalamic midline cell populations projecting to the nucleus accumbens, amygdala, and hippocampus in the rat. *J Comp Neurol* **297**: 582–593.
- Talvik-Lofti M, Nyberg S, Nordstrom AL, Ito H, Halldin C, Brunner F et al (2000). High 5-HT<sub>2A</sub> receptor occupancy in M100907-treated schizophrenia patients. *Psychopharmacology* **148**: 400–403.
- Tanaka E, North RA (1993). Actions of 5-hydroxytryptamine on neurons of the rat cingulate cortex. *J Neurophysiol* **69**: 1749–1757.
- Tandon R, Harrigan E, Zorn SH (1997). Ziprasidone: a novel antipsychotic with unique pharmacology and therapeutic potential. *J Serotonin Res* **4**: 159–177.
- van Hemert JCJ (1975). Pipamperone (Dipiperon, R3345) in troublesome mental retardates: a double-blind placebo-controlled cross-over study with long-term follow-up. *Acta Physiol Scand* **52**: 237–245.
- Van Renynghe de Voxvrie G, De Bie M (1976). Character neuroses and behavioural disorders in children: their treatment with pipamperone (Dipiperon): a clinical study. *Acta Psychiatr Belg* **76**: 688–694.
- Vickers SP, Easton N, Malcolm CS, Allen NH, Porter RH, Bickerdike MJ et al (2001). Modulation of 5-HT<sub>2A</sub> receptor-mediated head-twitch behavior in the rat by 5-HT<sub>2C</sub> receptor agonists. *Pharmacol Biochem Behav* **69**: 643–652.
- Wander TJ, Nelson A, Okazaki H, Richelson E (1986). Antagonism by antidepressants of serotonin S<sub>1</sub> and S<sub>2</sub> receptors of normal human brain *in vitro*. *Eur J Pharmacol* **132**: 115–121.
- Weiss EL, Potenza MN, McDougale CJ, Epperson CN (1999). Olanzapine addition to obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. *J Clin Psychiatry* **60**: 524–527.
- Willins DL, Meltzer HY (1997). Direct injection of 5-HT<sub>2A</sub> receptor agonists into the medial prefrontal cortex produces a head-twitch response in rats. *J Pharmacol Exp Ther* **282**: 699–706.