Co-administration of atypical antipsychotics and antidepressants disturbs contrast detection in schizophrenia

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Abstract

Atypical antipsychotics (APDs) antagonize both serotonin and dopamine receptors. This antagonism is, however, often confounded by co-administration of other medications, such as antidepressants, that affect pharmacological activity at these receptors. While it is known that the modulation of dopamine affects cognitive processes such as working memory, the interactions between APDs and antidepressants in behaviors including sensory processes are not clear. In this study, we investigated the effect of combined treatment with antidepressants and atypical antipsychotics on memory-related visual processing in schizophrenia. We employed (1) contrast detection, a task requiring the maintenance of visual signals over a short period of time; and (2) direction discrimination, a task not requiring maintenance of visual signals. On contrast detection, the performance was significantly worse in the patients taking both APDs and antidepressants than in patients taking just APDs. On direction discrimination, however, the performance did not differ between the patients taking just APD and those taking both APDs and antidepressants. Given that antidepressants interfere with APD’s stimulation of D1 receptors via agonism of serotonin receptors, the poor performance on contrast detection suggests that the interaction between these two types of psychotropic drugs selectively disrupts the sensory processes requiring retention of visual information.

Keywords: Antidepressant; Atypical antipsychotics; Visual processing; Working memory; Schizophrenia

1. Introduction

Polypharmacy is common in the treatment of schizophrenia. Often this polypharmacy is the result of secondary symptoms such as depressed mood. Indeed even considering the efficacy of medications such as atypical antipsychotics, depressed mood remains a common problem (Siris, 2000). Recent animal studies suggest that the modulation of serotonin via antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) interferes with the action of dopamine-serotonin interactions of atypical antipsychotics (APDs) (Ichikawa et al., 2001b; Weterink et al., 2001). In schizophrenic patients, cognitive performance was improved when a 5HT2a antagonist was added to typical antipsychotic treatment (Poyurovsky et al., 2003).
Animal research has revealed how APDs modulate different subtypes of dopamine and serotonin neurotransmitters. Several studies have found that APDs indirectly stimulate D1 receptors in the medial prefrontal cortex (Moghaddam and Bunney, 1990; Nomikos et al., 1994; Pehek and Yamamoto, 1994; Kuroki et al., 1999; Volonté et al., 1997; Rollema et al., 2000; Ichikawa et al., 2001a; Westerink et al., 2001). This indirect stimulation occurs through direct stimulation of 5HT1a-receptors by combined 5HT2a and D2 antagonism (Ichikawa et al., 2001a,b). This interaction may be illustrated as following:

\[-5\text{HT}_{2a} - D_2 \rightarrow 5\text{HT}_{1a} \uparrow \rightarrow D_1 \uparrow\]

It is important to point out here that neither D2 nor 5HT2a antagonism alone is sufficient to stimulate 5HT1a receptors, a precursor of D1 receptor stimulation; rather it is the combined antagonism of D2 and 5HT2a that indirectly results in the stimulation of D1 receptors (Kuroki et al., 1999; Rollema et al., 2000; Ichikawa et al., 2001a; Westerink et al., 2001).

The administration of 5HT2a agonists has been shown to block the stimulation of D1 receptors by APDs (Rollema et al., 2000; Ichikawa et al., 2001b; Westerink et al., 2001). Specifically, DOI, a 5HT2a/2c receptor agonist, attenuates stimulation of prefrontal dopamine receptors by clozapine (Ichikawa et al., 2001a). Many antidepressants such as SSRIs are 5HT2a agonists. Thus, in principle, combined treatment of these antidepressants and APDs in patients may interfere with APDs’ stimulation of D1 receptors. The interaction of antidepressants and APDs may be demonstrated as:

\[
\begin{array}{l}
\text{APD} - 5\text{HT}_{2a} - D_2 \rightarrow 5\text{HT}_{1a} \uparrow \rightarrow D_1 \uparrow \\
\text{Antidepressant} + 5\text{HT}_{2a} \\
\text{Combined} - D_2 \rightarrow 5\text{HT}_{1a} \uparrow \rightarrow D_1 \uparrow \\
\text{effect} \quad \text{(weakened to diminished stimulation)}
\end{array}
\]

That is to say, co-administration of antidepressants and APDs can decrease the ability of APDs to stimulate D1 receptors because of a canceling effect of antidepressants on the APDs’ antagonism of 5HT2a. In order to determine behavioral consequences of this co-administration of psychotropic drugs, we can examine visual and cognitive responses that are related to D1 modulation.

Evidence suggests that D1 receptor stimulation has a principal role in memory dependent visual tasks. For example, injection of D1 antagonists, SCH23390 and SCH39166, in prefrontal areas of monkeys induced errors and increase latency during performance of working memory tasks at delays as short as 1.5 s (e.g. Sawaguchi and Goldman-Rakic, 1994). Assuming that APDs ameliorate cortical hypo-dopaminergia in schizophrenia, the patients taking APDs should have improved or normalized performance on visual perception tasks requiring maintenance of visual signals. If this modulation of dopamine by APDs were blocked by the co-administration of antidepressants, then performance would be again impaired.

This study examines the effects of dopaminergic-serotonergic interaction on visual tasks that differ in memory requirements by testing schizophrenia patients taking both antidepressants and APDs and those taking only APDs. If antagonism of both 5HT2a and D2 receptors were necessary for stimulating 5HT1a and then D1 receptors, the combination of antidepressants and APDs would reduce the extent to which D1 receptors are stimulated. Because D1 receptor stimulation is important for working memory related tasks, patients taking APDs and antidepressants would be expected to perform worse on a task that requires maintenance of a visual signal, but perform similarly on a task that does not have such a requirement.

Finally, not all combinations of antidepressant and APD medications are expected to affect performance equally on memory-related tasks. Stimulation of D1 has been shown to depend on a relation of low D2 antagonism relative to 5HT2a antagonism. This relationship between D2 and 5HT2a antagonism suggests that each APD stimulates D1 receptors to different extents, depending on its relative potency as a D2 antagonist compared to its potency as a 5HT2a antagonist. For example, Rollema et al. (2000) found that at equal doses, clozapine, a relatively weak D2 as compared with 5HT2a antagonist, leads to greater stimulation of D1 receptors than does ziprasidone, which is a more potent D2 receptor antagonist. In addition, certain antidepressants exert effects not only on serotonin, but also on dopamine and norepinephrine. For these reasons, this study included only those subjects taking clozapine, olanzapine, or quetiapine.
for APDs, and trazadone, clomipramine or those in the class of SSRIs for antidepressants.

In Experiment 1, subjects preformed a contrast detection task that requires comparing visual signals in two consecutive time intervals. Maintenance of visual signals across two time intervals is necessary for performing the task. In Experiment 2, subjects performed a direction discrimination task, in addition to the contrast detection task. The direction discrimination task requires that subjects respond each time when a stimulus was presented. Thus, no maintenance of visual signals is necessary for performing this task.

1.1. Experiment 1

1.1.1. Methods

1.1.1.1. Subjects. Thirty-two schizophrenia patients and seventeen normal controls participated in this experiment. Eighteen patients were taking APDs (mean chlorpromazine hydrochloride dose equivalent (CPZ): 454.5 mg (σ = 245.7 mg)) and fourteen patients taking both APDs (CPZ: 643.5 mg (σ = 277.3 mg) and antidepressants. Four patients in the co-administration group were excluded because of the types of antidepressants they took (see above on this page). The remaining patients in the co-administration group were excluded because of the types of antidepressants they took (see above on this page). The remaining patients in the co-administration group took one of three SSRIs, Celexa (n = 2), Prozac (n = 2) and Zoloft (n = 6). Medications were prescribed independently of this research study. None of the normal controls were taking medication at the time of the study.

Patients were discharged during the past year from a psychiatric hospital and met DSM-IV criteria for schizophrenia or schizoaffective disorder. Patients were independently diagnosed before admittance into the study based upon review of Structured Clinical Interview for the DSM-IV (Spitzer et al., 1994) and evaluation of hospital records.

Subjects in each group were matched for age, sex, education and socio-economic status. The verbal IQ scores between two subject groups are slightly, but not significantly, different (p > 0.1), partly because of the small sample sizes in each group. We do not expect, however, that the intelligence scores have a substantial effect on visual sensory responses; which of course needs to be confirmed in future studies using a larger sample. Lastly, patients in each medication group did not differ in brief psychotic rating score (BPRS) (p > 0.1) (Table 1).

1.1.1.2. Stimuli. The target was a sinusoidal vertical grating with a spatial frequency of 0.5 cycles per degree. The gratings were moving at 5 Hz (10°/s) horizontally either to the right or to the left. The target was generated in a Macintosh computer (Quadra 600), and was presented within a circular aperture of 10° of visual angle.

1.1.1.3. Procedure. Contrast detection thresholds were determined using a two-alternative forced choice method (3 down/1 up ~ 79% correct). During each trial, each of two temporal intervals was signaled by a tone. The target appeared randomly at one interval across trials; dur-

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Verbal IQ</th>
<th>Age</th>
<th>Education (years)</th>
<th>BPRS a</th>
<th>SES b</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD + antidepressant</td>
<td>7F, 3M</td>
<td>94 (11.0)</td>
<td>41.7 (7.4)</td>
<td>13.5 (1.5)</td>
<td>42 (14.7)</td>
<td>I 10%</td>
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<td></td>
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<td></td>
<td></td>
<td>II 30%</td>
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<td></td>
<td></td>
<td>III 60%</td>
</tr>
<tr>
<td>APD</td>
<td>7F, 11M</td>
<td>105.3 (11.0)</td>
<td>35.0 (8.3)</td>
<td>14.6 (3.4)</td>
<td>37.9 (13.1)</td>
<td>I 33.3%</td>
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<td></td>
<td>II 33.3%</td>
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<td>III 27.8%</td>
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<td>V 6.6%</td>
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<td>I 17.6%</td>
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<td></td>
<td>II 35.3%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>III 47.1%</td>
</tr>
<tr>
<td>NC</td>
<td>13F, 4M</td>
<td>102.6 (11.3)</td>
<td>37.5 (8.8)</td>
<td>14.8 (2.8)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

a BPRS—brief psychiatric rating scale.

b SES—socioeconomic status.
ing the alternate interval a blank screen with a luminance equal to the target was presented. Subject’s task was to indicate if the target came during the first or second interval. Their responses were given by pressing one of two designated keys on a computer keyboard. Each of the two intervals lasted 300 ms followed by an inter-trial interval of 450 ms. The level of contrast was determined by the staircase method, and was decreased by 5% of current level for each set of three consecutive correct responses, or increased by 5% for each incorrect response. Instruction and a practice session were provided prior to data collection. Experimenters were blind to diagnostic and medication condition of the subjects during testing.

1.1.1.4. Results. Contrast detection thresholds were significantly higher in schizophrenic patients taking both antidepressants and APDs (0.0047, \( \sigma = 0.0019 \)) than those of patients taking only APDs (0.0019, \( \sigma = 0.0011 \)) \( (t_{(25,1)} = 4.26, p < 0.01) \) and than normal controls (0.0021, \( \sigma = 0.0010 \)) \( (t_{(25,1)} = 4.01, p < 0.01) \). There was no significant group difference between patients taking only APD medication and normal controls \( (t_{(32,1)} = 0.55, p > 0.1) \) (Fig. 1).

The threshold elevation in the patients taking both drugs was not related to their psychosis, as BPRS scores between the two patient groups did not differ \( (t_{(26,1)} = 0.76, p > 0.1) \) and contrast detection thresholds were not correlated with BPRS scores \( (r = 0.16, p > 0.1) \). It is unclear, however, the BPRS scores in the two patient groups were similar before the drugs were administered. In future studies, comparing contrast detection performance before and after the drug treatments may elicit the effect on a relation of behavioral responses (such as contrast detection) and psychotic status (measured by BPRS scores) in patients. The correlation between contrast detection threshold and dose of atypical antipsychotics, expressed as CPZ equivalents, was 0.24 \( (p > 0.05) \) in the patients taking APDs only. The contrast detection thresholds were 0.0042, 0.0061, and 0.0043 in the patients taking Celexa \( (n = 2) \), Prozac \( (n = 2) \) and Zoloft \( (n = 6) \), respectively.

The poor performance on contrast detection, as indicated by high thresholds, may be attributed to two processes that are required for performing this task. First, encoding of contrast signals is required in order to detect the visual target (gratings). Second, maintenance of the visual signal over two time intervals is also required in order to indicate in which interval the target is present. To determine which process is primarily affected by the co-administration of antidepressant and APD drugs, we conducted another experiment, in which a visual direction discrimination task was used. This direction discrimination task is

Fig. 1. Group thresholds in contrast detection. Three subject groups are included—normal controls (NC) \( (n = 17) \), schizophrenic patients taking both atypical antipsychotic drugs (APD) and antidepressants (SZ (APD + antidepressant)) \( (n = 10) \), and schizophrenic patients taking just APD (SZ (APD)) \( (n = 18) \). The thresholds are represented on ordinate. High threshold values mean poor performance. The error bars indicate \( \pm 1 \) standard deviation.
comparable to the contrast detection task in encoding process, as it applies the same visual target whose contrast is modulated. It does not, however, require maintenance of visual signals over time.

1.2. Experiment 2

1.2.1. Methods

1.2.1.1. Subjects. Fourteen schizophrenia patients participated in this experiment. Eight patients were taking APDs and six taking a combination of APDs and antidepressants. Medications were prescribed independently of this research study.

Recruitment and ascertainment of the patients were similar those used in Experiment 1. The patients in the two medication groups were matched for age, sex, education and socio-economic status, and scores for BPRS \( p>0.1 \) (Table 2).

1.2.1.2. Stimuli. The target was similar to that used in Experiment 1 except that the direction of motion was either leftward or rightward, randomized from trial to trial (see procedure below).

1.2.1.3. Procedure. Experiment 2 implemented contrast detection as explained in Experiment 1. The procedure for direction discrimination was sim-
ilar to that used in Experiment 1 except for following changes. First, each trial consisted of one time interval and the target was present in each interval (trial). Second, the subject’s task was to indicate the direction of the moving target (left or right) each trial as it appeared. Thus, maintenance of visual signals over time was not necessary for performing the task.

2. Results

Direction discrimination thresholds did not differ significantly between the patients taking antidepressant and APD drugs (0.0018, $\sigma = 0.0005$) and those taking only APDs (0.0015, $\sigma = 0.0006$) ($t_{(12,1)} = 1.15, p>0.1$). Contrast detection thresholds, however, were again significantly elevated in the patients taking APDs and antidepressant (0.012, $\sigma = 0.017$), compared with those taking just APDs (0.0014, $\sigma = 0.003$) (Wilcoxon Rank Sum $t_{(12,1)} = 69, p<0.01$) (Fig. 2).

The group difference in contrast detection threshold was not related to patients’ illness severity as BPRS scores were not significantly different between the patients taking antidepressant and APD medication and those taking just APD drugs ($t_{(12,1)} = 0.52, p>0.1$).

Neither contrast detection thresholds nor direction discrimination thresholds were correlated with BPRS scores ($r = 0.07, p>0.1$ and $r = -0.45, p>0.05$, respectively). The two patient groups were similar in the composition of schizophrenia or schizoaffective disorder patients.

3. Discussion

The two experiments showed that combined treatment of antidepressant and APD medications made schizophrenia patients perform poorly on a contrast detection task that requires maintenance of visual signals over a short period of time. The results of these experiments are consistent with the notion that modulation of dopamine and serotonin plays an important role in memory-related visual and cognitive processing. Obviously, this study had modest sample sizes, which calls a replication of its results in a larger group of subjects, but it nevertheless provides empirical evidence for a confounded effect of combined treatment of antidepressants and APDs at behavioral level. Moreover, in direction discrimination, a task not requiring maintenance of visual signals, the patients taking both APDs and antidepressants and those taking only APDs did not differ in performance. The result from this control task suggests that the adverse effect of combining antidepressant and APD is specific to the visual processes that involve memory. Below we discuss several possible explanations of the findings and their implications for the effect of an interaction of antidepressants and APDs on visual responses of schizophrenia patients. More broadly, the results of this study suggest that a combined use of APDs and antidepressants has unwanted consequence in memory-related behaviors.

First, schizophrenia patients performed normally on direction discrimination whether they took both antidepressant and APD medications or just APDs. Because direction discrimination and contrast detection used similar visual targets and experimental procedures, the impaired contrast detection found in the patients taking both antidepressant and APD medications cannot be attributed to a generalized deficit associated with schizophrenia. The generalized deficit explanation is also inconsistent with the fact that the patients’ performance and their illness severity, as measured by BPRS, were not correlated.

Second, the pharmacological effect of combining APD with antidepressant medication, as compared with using APD alone, differs in the extent to which $D_1$ receptors are stimulated. Administration of an APD alone leads to more stimulation of $D_1$ receptor than does co-administration of two drugs; combined use of the two psychotropic drugs attenuates the antagonism of $5HT_{2A}$, thus resulting in less $D_1$ receptor stimulation. There may be a conceptual gap in applying contrast detection to understand the drug effect, as it is generally believed that this task is mediated in the occipital cortex if not earlier. In other words, visual processing of contrast may have been completed before it reaches the prefrontal cortex, the site at which modulation of $D_1$ receptors occurs and working memory is mediated. However, the requirement of maintaining visual signals over time in the contrast detection task suggests an involvement of not only sensory but also working memory processes.
Third, schizophrenia patients show spatial working memory deficits (e.g. Park and Holzman, 1992). Can the contrast detection deficit, found in the patients of this study, be considered as a working memory problem? Spatial working memory operates on a time scale of several to several tens of seconds, during which information needs to be maintained on-line for further processing and recall. In the contrast detection task, visual information was maintained for less than one second. To understand the contrast detection deficit found in this study and the spatial working memory deficit reported in schizophrenic patients, we need to consider a brain mechanism that is separate from, but related to, the one underlying spatial working memory. One candidate is the iconic memory store, a short-term memory component important for maintaining basic features of visual stimuli including contrast (Magnussen, 2000).

Fourth, working memory may be modulated by neurotransmission in various ways. The working memory process can be mediated in different cortical areas, depending on the nature of information and the time scale on which the information is held. Indeed, in the primary visual cortex, not only sensory but also delayed responses to visual signals have been recorded. The time scale of the delayed neuronal responses was between 500 ms and 1 s (Super et al., 2001). It appears that the range of time required for holding visual information in the contrast detection task is similar to the range of time in the delayed neuronal responses reported in visual cortex (Super et al., 2001). Therefore, the contrast detection deficit, caused by the combined use of antidepressant and APD, may be more related to the short-term memory storage of visual signals in primary visual cortex.

While we do not have much knowledge about the interaction of serotonin and dopamine in the primary visual cortex, we do know that feedback from other cortical areas plays an important role in determining neuronal responses from this area (Foxe and Simpson, 2002; Super et al., 2001). Two possible mechanisms may underlie the effect of co-administration of APD and antidepressant medications on contrast detection in schizophrenia patients. First, a disruption of the APDs’ antagonism of D2 and 5HT2a by antidepressants occurs in the cortical areas beyond the primary visual cortex. Through a feedback mechanism, the disruption in these higher areas may alter the neuronal responses in the primary visual cortex, the site where contrast detection is accomplished.

This visual feedback mechanism may bridge the gap between visual processing in the occipital areas and working memory in the prefrontal areas. Foxe and Simpson (2002) indicate that feedback to the primary visual cortex from parietal and prefrontal areas can occur as quickly as 30 ms. In that study, the P1 and N1 recorded in ERP actually represent late, rather than early visual processing, unlike originally assumed. The notion that a feedback mechanism may provide a common link between working memory and visual processing appears to be a plausible interpretation for the results of this study.

The co-administration of APD and antidepressant medications acts to attenuate the magnitude of regulation of D1 receptors that occurs when APDs are administered alone. This attenuation may occur in the prefrontal areas, because of the prominence of both serotonin and dopamine receptors in this cortical area. If so, the attenuation of D1 stimulation in the prefrontal areas would send a signal back to the visual areas, the location where visual working memory is based.

In this study, we showed that co-administration of antidepressant and APD produced poor performance only on a visual task that requires maintenance of visual signals. Insomuch as behavioral responses and quality of life in schizophrenic patients are interrelated (Green, 1996), any strategy for drug treatment should take into account not only psychotic status but also other factors such as sensory functions. We suggest that given the fast dynamics of atypical antipsychotic drugs (Seeman and Tallerico, 1999), it may be possible to reduce the interaction of atypical antipsychotic and antidepressant drugs. Specifically, patients should be aware of the unwanted side-effect on visual perception, as shown in this paper, and consider taking antidepressants and atypical antipsychotic drugs, when needed, separately, i.e., allowing the effect of atypical antipsychotic drugs largely to dissipate before administering antidepressants. Patients may also consider selecting those antidepressants that do not act on 5HT2a receptors (e.g. Wellbutrin), if they also need to...
take atypical antipsychotic drugs. In this regard, it is useful to study whether 5HT2a alone has an effect on memory-related visual functions, which could be done in depressed but not schizophrenic patients who take only antidepressants.

Since there is evidence for the involvement of D1 receptors in the prefrontal cortex even at a delay of 1–1.5 s (Sawaguchi and Goldman-Rakic, 1994; Aultman and Moghaddam, 2001), the possibility of interpreting the effect of co-administration of APD and antidepressant medication based on prefrontal mechanisms cannot be excluded. Further research into the existence of such a mechanism, its time course, and its function is needed.

The actions of antipsychotic drugs involve complex neurochemical and neurophysiological processes. In one study, we showed that antipsychotic drugs have little effect on motion discrimination (Chen et al., 1999). In another study, we found that schizophrenia patients taking APDs performed normally on a contrast detection task while patients taking typical antipsychotics preformed deficiently (Chen et al., 2003). Combination of different types of psychotropic drugs is an even more complicated issue. It remains to be seen whether the combined treatment of APD and antidepressant medication affects other memory-related sensory, motor, and cognitive processing.

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References


Seeman, P., Tallierco, T., 1999. Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor


