1.1. Aripiprazole and aggravated psychosis

Introduction
Aripiprazole is an atypical antipsychotic drug which acts through a combination of partial agonism at dopamine D2- and serotonin 5-HT1a receptors and antagonism of serotonin 5-HT2a receptors. Aripiprazole has been approved for the Dutch market since June 2004 and is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older. It is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. The most frequent psychiatric adverse events reported are restlessness, insomnia and anxiety. Post-marketing surveillance showed also agitation and nervousness. The current observation describes the association between aripiprazole and aggravation of psychotic disorder [1].

Aripiprazole is available as Abilify® (orodispersable) tablets (5, 10, 15, 30 mg), oral solution 1mg/ml and solution for injection 7.5 mg/ml [1].

Reports
On August 1, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained 6 reports concerning aggravated psychosis associated with the use of aripiprazole. The reports are listed in Table 1. All cases were reported by physicians; in three of these, cases were reported via the manufacturer. All cases involved men, aged between 25 and 49 years; for one case the age was not reported (case C). In four patients aripiprazole was used for schizophrenia, in two patients for psychosis. In three cases the latency was several days, in the three other cases the latency was unknown. One patient had recovered after discontinuation of aripiprazole, one was recovering; one had not recovered, and for the other two patients the outcome was unknown.

Table 1. Reports of aggravated psychosis associated with the use of aripiprazole

<table>
<thead>
<tr>
<th>Patient, Number, Sex, age, Reporter</th>
<th>Drug, daily dose Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset Action with drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 47861 M, 41-50 years pharmaceutical company</td>
<td>aripiprazole 15mg schizophrenia</td>
<td>testosterone zopiclon</td>
<td>psychotic reaction nos 4 day discontinued</td>
<td>not recovered</td>
<td></td>
</tr>
<tr>
<td>B 48296 M, 21-30 years specialist doctor</td>
<td>aripiprazole 10mg schizophrenia, paranoid type</td>
<td>clozapine oxazepam bipiridene metoclopramide</td>
<td>drug maladministration, psychosis aggravated</td>
<td>not reported unknown unknown</td>
<td></td>
</tr>
<tr>
<td>C 56544 M, unknown pharmaceutical company</td>
<td>aripiprazole 15mg schizoaffective disorder</td>
<td>not reported</td>
<td>psychotic disorder nos</td>
<td>not reported unknown unknown</td>
<td></td>
</tr>
<tr>
<td>D 57159</td>
<td>aripiprazole 15mg lithium carbonate</td>
<td></td>
<td>psychotic disorder 2-3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient, Number, Sex, age, Reporter</td>
<td>Drug, daily dose Indication for use</td>
<td>Concomitant medication</td>
<td>Suspected adverse drug reaction</td>
<td>Time to onset Action with drug</td>
<td>Outcome</td>
</tr>
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</tr>
<tr>
<td>M, 41-50 years pharmaceutical company</td>
<td>schizoaffective type of psychosis</td>
<td>valproate alprazolam risperidon</td>
<td>nos, fatigue</td>
<td>discontinued</td>
<td>unknown</td>
</tr>
<tr>
<td>E 89052 M, 31-40 years specialist doctor</td>
<td>aripiprazole 30mg psychosis</td>
<td>oxazepam lorazepam</td>
<td>(florid) psychosis</td>
<td>not reported</td>
<td>discontinued</td>
</tr>
<tr>
<td>F 112067 M, 31-40 years specialist doctor</td>
<td>aripiprazole 15mg psychosis</td>
<td>clozapine fluvoxamine</td>
<td>psychosis aggravated</td>
<td>2 day</td>
<td>discontinued</td>
</tr>
</tbody>
</table>

Additional information on the reported cases:
Patient B suffered from an aggravated psychosis probably due to aripiprazole and withdrew from treatment and started wandering. The concomitantly used clozapine had already been gradually withdrawn. For the remaining concomitant medication (biperidene, oxazepam, metoclopramide) continuation was unknown.

In first instance patient C had diminished symptoms of restlessness and showed more coherent behaviour after initiation of aripiprazole. In the past the patient had already received treatment for schizoaffective disorder with risperidone, lithium and sodium valproate. The patient was a drug abuser who uses cocaine and marijuana.

In the past patient E had been successfully treated with aripiprazole 15 mg daily, after a while the drug was withdrawn. After withdrawal the patient again developed psychosis, and aripiprazole was re-started. During 6 weeks the dose was ultimately increased to 30mg/day. The reported adverse drug reaction was a (florid) psychosis following this re-administration of aripiprazole. Finally, aripiprazole was discontinued, the patient was treated with olanzapine and recovered. Patient was known with schizophrenia.

Patient F was hospitalised, because of aggravated psychosis and aripiprazole was discontinued, furthermore the patient was treated with alprazolam. The medical history indicated that the patient suffered from schizophrenia.

**Other sources of information**

*SmPC*

Aggravation of psychosis is not mentioned in the SmPC of aripiprazole (Abilify®) [1]. Restlessness is described in 1-10% of patients, whereas agitation and nervousness have been reported during post-marketing surveillance.

*Literature*

Worsening or aggravation of psychosis after initiation of aripiprazole treatment has been described several times in literature [2-10]. In all of these cases, aripiprazole was started as substitution or add-on treatment after long-lasting treatment with other antipsychotic therapy. In most cases psychotic symptoms
(hallucinations, paranoid symptoms, delusions, aggressiveness, agitation) became apparent between 3 days and 4 weeks after start of aripiprazole in daily doses between 7.5 and 20 mg. All patients recovered in days to weeks after discontinuation of aripiprazole, either without [2,3] or with starting additional antipsychotic treatment or increasing the dose of concomitant antipsychotics. In several patients a positive rechallenge was observed [3-5,11]. Remarkably, in a treatment-naïve male of 23 year old male, aripiprazole 10 mg/day was first used successfully as initial antipsychotic treatment for paranoid schizophrenia [11]. After recovery, treatment was abandoned for several months. A relapse of symptoms several months later was treated with amisulpiride and biperidene. On patient’s wish aripiprazole was re-started 10 mg /day after several weeks, titrated to 20 mg/day in two weeks time. After three days he suffered from auditory hallucinations and feeling of strangeness and perplexity. Discontinuation resulted in subsiding of symptoms, re-starting in increase of auditory hallucinations.

Selvaray described a new onset psychosis with auditory hallucinations, paranoid thoughts and suicidal ideation three days after the start of aripiprazole 2 mg/day in a depressive 49-year-old woman, who had used duloxetine 40 mg twice daily for 7 months. Dose reduction of aripiprazole resulted in amelioration of her hallucinations, subsequent discontinuation led to a complete resolution of psychotic symptoms and suicidal ideation. There was no history of psychosis in the past or a family history of psychosis. Of further interest in this publication is the possible pharmacokinetic interaction between chronically used duloxetine, a CYP 2D6 inhibitor and aripiprazole, a substance for CYP 2D6, which might have resulted in higher serum levels of aripiprazole [12].

Another raise of aripiprazole serum levels has been suggested in the case of concomitantly used antipsychotics, which also act as substrates for CYP 2D6, including haloperidol. By competition between this drug and aripiprazol for CYP 2D6 binding sites, the serum level of both drugs might be raised [10].

Databases
On August 1, 2011, the database of the Netherlands Pharmacovigilance Centre contained six reports of aggravated psychosis in association with aripiprazole with a Reporting Odds Ratio (ROR) of 12.4 (95% CI 5.5 - 28.2), which was disproportional.
The WHO database of the Uppsala Monitoring Centre contained 446 reports of psychotic disorder in association with aripiprazole with a ROR of 11.6 (95 % CI 10.5 - 12.7).

On August 15, 2011, the Eudravigilance database contained 281 reports of psychotic disorder associated with the use of aripiprazole, which was reported disproportionally (ROR = 10.9, 95% CI: 9.7 – 12.3). It concerns 137 females and 122 males. In 22 cases, the patient’s sex was not reported. The median age of the patients was 34 years (range 9 – 82 years). A total of 272 reports were classified as serious, five were non-serious and in four cases the seriousness was not reported. In eleven cases, the criterion for seriousness was death.

Prescription data
The number of patients using aripiprazole in the Netherlands is shown in table 2 [13].
Table 2. Number of patients using aripiprazole in the Netherlands between 2006 and 2010

<table>
<thead>
<tr>
<th>Drug</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>5,811</td>
<td>6,692</td>
<td>8,195</td>
<td>10,526</td>
<td>12,977</td>
</tr>
</tbody>
</table>

**Mechanism**

Aripiprazole is an atypical antipsychotic agent (quinolinone derivative). It exhibits relatively high affinity for dopamine D2 and D3 receptors and serotonin 5-HT1A and 5-HT2A receptors. The efficacy of the drug in schizophrenia appears related to partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors has also been speculated [1]. It is a functional D2-antagonist under hyperdopaminergic conditions, but a functional D2-agonist under hypodopaminergic conditions [6,8].

Previous chronic administration of other antipsychotic drugs can decrease dopamine neurotransmission, resulting in an increase in dopamine receptor number (‘up-regulation’) and sensitivity [2]. In this hypodopaminergic state, initiation of aripiprazole might enhance dopamine neurotransmission due to the drug’s D2-agonistic effect on hypersensitive postsynaptic D2-receptors [3]. This hypothesis is supported by the fact that a treatment-naïve patient showed a good response on initial aripiprazole treatment [11]. After treatment with another antipsychotic with a high D2-antagonist activity, a second (and third) exposure to aripiprazole contrarily resulted in aggravation of psychotic symptoms. Another explanation is that aripiprazole is a weaker D2-antagonist than several other antipsychotics, for example risperidone; displacement of concomitantly used risperidone from the D2 receptors by aripiprazole, leads to a decreased D2 blockade, resulting in worsened symptoms [3].

The difference in time course of the emerging psychotic symptoms after start of aripiprazole, as observed in several case reports discussed above, may be due to the use of diverse concomitantly used antipsychotics. These concomitant drugs might have differences in the tenacity of binding at the dopamine receptor site in competition with aripiprazole [10].

**Discussion and Conclusion**

In the SmPC restlessness, a common reaction, and agitation or nervousness have been observed as reactions in association with aripiprazole treatment. These reactions were reported several times to Lareb. Beside these, Lareb received six reports of aggravated psychosis with the use of aripiprazole. Although confounding by indication cannot be ruled out, in most patients symptoms became worse within a few days after the start of aripiprazole. In two cases symptoms improved after discontinuation of aripiprazole (and treatment with olanzapine and alprazolam respectively). In four of the cases reported to Lareb the patients had used antipsychotic treatment in the past and/or used concomitant antipsychotic treatment. Both latency and use of previous/concomitant medication is in accordance with the observations in the literature.

As in the publication of Adan [11], patient E reacted well on aripiprazole in first instance. It is not known whether this patient used other antipsychotics, which might lead to up-regulation of D2 receptors and higher sensitivity, between the first and second treatment period with aripiprazole.
In patients D and F a competition between aripiprazole and concomitantly used medication (risperidone, fluvoxamine) for the CYP 2D6 binding sites might have played a role, as was observed in the publication DeQuardo [10].

In addition this association was supported by a statistically significant disproportionality in the Lareb-, the WHO- and Eudravigilance databases. A substantial number of publications in the literature confirmed the occurrence of exacerbation of psychotic symptoms after initiation of aripiprazole. This reaction might be due to the partial agonistic activity at the dopamine D2 receptor. On the clinical level the response may depend on several factors, including previously, and concomitantly used antipsychotic treatment. To minimize risks, caution is warranted in using aripiprazole as substitute for, or add-on treatment to, other antipsychotics. In the latter case it is recommended to start with a low dose (2.5-5 mg/day) of aripiprazole and closely monitor patients during titration [3,5].

- Possible new signal of aggravated psychosis in association with the use of aripiprazole.
  Attention to this association in Periodic Safety Updates may be warranted.

References

This signal has been raised on November 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).