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Treatment of Antipsychotic-Induced Hyperprolactinemia: An Update on the Role of the Dopaminergic Receptors D2 Partial Agonist Aripiprazole

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Abstract: Hyperprolactinemia is an unwanted adverse effect present in several typical and atypical antipsychotics. Aripiprazole is a drug with partial agonist activity at the level of dopamine receptors D2, which may be effective for antipsychotic-induced hyperprolactinemia. Therefore, we analyzed the literature concerning the treatment of antipsychotic-induced hyperprolactinemia with aripiprazole by updating a previous paper written on the same topic. More recent studies were reviewed. They showed that there are two options for the treatment of antipsychotic-induced hyperprolactinemia with aripiprazole. The safest strategy may require the addition of aripiprazole to ongoing treatments, in the case patients had previously responded to antipsychotic drugs and then developed hyperprolactinemia. However, it is advisable to monitor the patients in case relapses and/or side effect, although rare, might occur. Switching drugs should be considered when a patient does not appear to be responding to the previous antipsychotic, thus developing hyperprolactinemia. A cross-taper switch should always be considered, but the risk of a relapse in the disorder may occur more frequently and the patients should be closely monitored. However, limitations must be considered and further studies are needed to definitely elucidate this important issue. Some relevant patents are also described in this review.

Keywords: Add-on, antipsychotics, aripiprazole, dopamine, hyperprolactinaemia, partial agonism, prolactin, switch, update.

INTRODUCTION

Schizophrenia is considered to be among the most severe, debilitating and persistent of all psychiatric disorders [1]. Although the adult prevalence is approximately 1%, studies have indicated that sufferers constitute close to 10% of the permanently disabled population [2]. As such, schizophrenia is a major public health problem and the negative economic consequences underscore the urgent need to develop strategies to improve treatment effectiveness [3].

The treatment of schizophrenia habitually considers the long-term administration of antipsychotics drugs that have, more or less, the capability to block the dopaminergic D2 receptors [4]. Even if the antipsychotic action on the dopaminergic neurons in mesolimbic and mesocortical brain areas may improve symptoms, these drugs can cause unwanted side effects related to dopamine D2 blockade itself in non-mesolimbic regions such as extrapyramidal side effects (EPS, such as dystonias, parkinsonism, and akathisia) and hyperprolactinaemia [5]. This is because the atypical antipsychotics differing considerable in their receptor binding profile and systemic actions [6]. In fact, they significantly differ in their tendency to cause cardiovascular adverse events, weight gain, metabolic syndrome, EPS, QTc tract prolongation [7-9] and, at least theoretically, in their impact on various disease dimensions as positive symptoms, negative symptoms, cognitive symptoms and neurological soft signs [10-13].

Hyperprolactinemia is an unwanted adverse effect of most of conventional antipsychotics, but also of several atypical antipsychotics (especially amisulpiride, risperidone and paliperidone), and health professionals often do not make a diagnosis of antipsychotic induced hyperprolactinemia unless it becomes symptomatic [14]. As suggested by

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Citrome [15], even if the guidelines concerning the monitoring of hyperprolactinemia in patients who are treated with antipsychotics are somewhat limited, a careful clinician should measure a baseline level of prolactin in the plasma and follow-up at least once when starting any patient on a typical or atypical antipsychotic drug. Hyperprolactinemia is associated with negative impact on sexual and reproductive function and this may be often the cause of treatment discontinuation and psychotic relapse [16]. In addition, antipsychotic-induced hyperprolactinemia implies important long-term effects, such as osteoporosis with and increased risk fracture and higher risk of developing breast and prostate cancer [17,18]. Moreover, in some patients, hyperprolactinemia may predispose to the development and progression of autoimmune disorders of endocrine glands [19]. Concerning antipsychotic-induced hyperprolactinemia, its relative incidence may roughly be explained by their potency as D2 antagonists (Table **1**) [14].

There are several strategies in the treatment of antipsychotic-induced hyperprolactinemia, such as the decreasing of the antipsychotic doses or the switching of the antipsychotic drugs [15]. Also, the addition of a dopaminergic agonist [20] could offer a solution.

Aripiprazole is an antipsychotic drug with a unique pharmacological profile, as is, to date, the only available partial agonist to the dopamine D2 receptors [21]. Aripiprazole is approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia, bipolar mania, and bipolar maintenance therapy and is widely used in such disorders with good results [22]. Aripiprazole has the same efficacy when compared to other atypical antipsychotics [22] and has little effect on the blood pressure, Q-Tc interval, serum glucose and lipids, weight and prolactin levels with lower propensity to cause prolactin-related sexual dysfunctions [23]. The most common adverse effects of aripiprazole are headache, anxiety, insomnia, dizziness and akathisia [24].

In a previous paper published in 2010 by our research group on Recent Patents on Endocrine, Metabolic & Immune Drug Discovery [25], we analyzed the literature concerning the treatment of antipsychotic-induced hyperprolactinemia with aripiprazole add-on or switch. However, since the paper has been first published, the literature on the matter has known a rapid increase, therefore making necessary the present mini-review. The paper will provide an update on this topic, by analyzing the Medline, PsycInfo, Embase databases from January 2010 through August 2013, in order to update and integrate the originally reviewed literature mentioned in the previous paper [22]. We found 13 published papers and all were included in the present review.

TREATMENT OF ANTIPSYCHOTIC-INDUCED HYPERPROLACTINEMIA WITH ARIPIPRAZOLE: AN UPDATE

Several new reports have shown that aripiprazole may be a valuable option in the treatment of antipsychotic-induced hyperprolactinemia [22]. In these cases, aripiprazole can be prescribed in two different ways: 1) as add-on to the ongoing antipsychotic treatment or 2) conducting a switch from the first agent to aripiprazole, usually in case of non-response and development of hyperprolactinemia (As shown in Table **2**).

1. Aripiprazole Add-on.

Until 2010, a number of studies have shown the reversal of antipsychotic-induced hyperprolactinemia after addition of aripiprazole. The antipsychotic involved were oral and decanoate haloperidol [26, 27], risperidone long acting injectable (RLAI) [28], oral risperidone [29, 30], paliperidone, risperidone and quetiapine [31], olanzapine [32]. Moreover, several randomized, double-blind, placebo-controlled studies [33-35] showed improvement in prolactin levels by adjunctive aripiprazole in patients maintained with another antipsychotic. A post hoc analysis of published studies involving switching from risperidone or olanzapine showed a reduction on prolactin values during the first week of the switch, when aripiprazole was administered together with risperidone or olanzapine [36].

From 2010 several case reports and case series, four open label studies and one RCT have been published. Case reports confirmed the beneficial effect of aripiprazole add-on on prolactin levels in patients treated with zuclopenthixol decanoate [37], risperidone [34], risperidone long-acting injections (RLAI) [34, 38], paliperidone [39] and blonanserin [40]. Concerning open label studies, Chen *et al.* [41] administered a flexible dosage of aripiprazole (5-20 mg/day) to 24 patients with antipsychotic-induced hyperprolactinemia and found that aripiprazole add-on was beneficial not only in reducing prolactin levels, but also improved psychotic symptoms as measured by Positive and Negative Syndrome Scale (PANSS). These finding were also confirmed by Yasui-Furukori *et al.* [42] in female patients with schizophrenia and risperidone-induced hyperprolactinemia, even when a low dosage (3 mg/day) of aripiprazole was used with a plateau at dosages beyond 6 mg/day. Moreover, as schizophrenic patient may require a long-acting depot antipsychotic due to poor compliance and one of the most used, RLAI, is commonly associated with prolactin elevation, van Kooten *et al.* [43] added openly aripiprazole 10 mg/day in patient with RLAI-induced hyperprolactinemia and found that, in twelve patients with a long duration of illness and an average of 3.6 years of RLAI treatment, aripiprazole add-on was effective in reducing and/or normalizing prolacting levels without worsening of psychotic symptoms. This finding was recently confirmed by Trives *et al.* [44] who demonstrated that the addition of aripiprazole 5 mg daily to RLAI was associated with a significant decrease in hyperprolactinemia levels with no worsening of disease.

Nevertheless, it should be noted, however, that a case report showed a lack of the expected decrease of serum prolactin levels by adding aripiprazole in a patient treated with amisulpride [45]. In the open label study of Chen *et al.* [29], this observation was somewhat confirmed supporting the notion of a superior efficacy of aripiprazole in treating

risperidone-induced hyperprolactinemia than that induced by benzamides (amisulpride and sulpride).

The only double-blind, placebo-controlled randomized trial (RCT) published after the 2010 was that of Lee *et al.* [46] who enrolled 35 subjects stabilized on risperidone, randomly assigned to receive 10 mg/day aripiprazole (n = 17) or placebo (n = 18) for 12 weeks and an open-label phase for another 12 weeks whereas the aripiprazole group received a flexible dose of aripiprazole while tapering risperidone. The found that, even if adjunctive treatment with and switching to aripiprazole were not associated with improved cognitive function in patients with schizophrenia receiving risperidone, aripiprazole treatment significantly decreased negative symptoms and lowered -induced hyperprolactinemia.

However, to date, even if aripiprazole add-on was proven to be effective to treat antipsychotic-induced hyperprolactinemia, caution is always required when a patient is prescribed an antipsychotic polypharmacy drug, as there is evidence suggesting that polypharmacotherapy might be associated with increased adverse effects as well as mortality, as a possible development of metabolic syndrome and reduced cognitive functions compared with monotherapy [47, 48]. However, such risks are demonstrated to be lower in the case of aripiprazole add-on [49, 50].

2. Switch to Aripiprazole

Until 2010, the effects of switching to aripiprazole from other antipsychotics in schizophrenic, schizoaffective or bipolar disorder patients with antipsychotic-induced hyperprolactinemia have been shown in several case reports and open label trials mostly involving switches from haloperidol, ziprasidone, sulpride, amisulpride, zuclopenthixole and risperidone [51-57]. However, the switching strategy may be potentially harmful as, in some of these studies, it have been reported cases of re-emerging or worsening of psychotic symptoms during the switching to aripiprazole or unwanted side effects such as insomnia, nausea, vomiting, anxiety, and agitation [52]. Therefore, it was recommended that the switch strategy should be used with caution [58]. It is possible that an abrupt switch to aripiprazole may worsen the psychotic symptoms because of the relative increase in dopaminergic transmission mediated by its dopamine D2 receptor agonist properties [59]. Moreover, aripiprazole may not be suitable in terms of response and/or symptoms control than other antipsychotics and this should be taken into account in case of switch [60-63]. If switching to aripiprazole, patients are advised to gradually discontinue the existing antipsychotic agent, in order to prevent the worsening of the psychotic symptoms [55].

From 2010 onwards, only four studies (two case report, one case series and one open label study) have been published on switching to aripiprazole in psychiatric patients with antipsychotic-induced hyperprolactinemia. Kuloglu *et al.* [64] described a case series of five female schizophrenic inpatients that developed symptomatic hyperprolactinemia and psychotic exacerbation while taking typical (zuclopentixol) or atypical (risperidone) antipsychotic drugs who were gradually and successfully switched to aripiprazole (20-25 mg/day). All patients had, after the switch, a normalization of prolactin levels and gained also an improvement of psychiatric symptoms as measured by the PANSS and the Brief Psychiatric Rating Scale (BPRS), without serious adverse effects during, or after, the switching process. These findings were also confirmed by the case report described by Broekhof *et al.* [65] where a female patient with psychosis, moderate mental retardation and pituitary adenoma with hyperprolactinemia was switched from risperidone to aripiprazole before beginning a therapy with a dopamine agonist (quinagolide). A reduction in serum prolactin levels, tumor size and visual field defects was observed in such patient without psychotic relapse. Wix-Ramos *et al.* [66] described the case of a young male patient with a pituitary micro adenoma as well as mental and behavioral disorders treated with haloperidol, carbamazepine and levomepromazine. He developed hyperprolactinemia and mammary hypertrophy, which improved when the patients switched to aripiprazole.

In 2012, Ishitobi *et al.* [67] conducted an interesting prospective, 12-week, open-label study on nine male subjects with autism spectrum disorders (ASDs) examining the efficacy and the tolerability of aripiprazole switched from risperidone. They found that serum prolactin levels decreased significantly from 17.3 $\pm$ 9.4 ng/mL to 2.3 $\pm$ 1.7 ng/mL, considering whole sample. In three male subjects who were showing hyperprolactinemia, the serum prolactin levels normalized after switching to aripiprazole.

Taken together, these findings suggest that the switching strategy should be considered when a patient did not respond to another antipsychotic and developed hyperprolactinemia [68]. However, the findings suggest that strategies involving tapering off of the previous treatment for switching patients to aripiprazole were preferable to abrupt discontinuation strategies, in order to prevent early worsening of symptoms and the premature discontinuation of treatment [69].

3. Meta-analyses

To date, there is only one meta-analysis of RCTs that compared the safety and efficacy of adjunctive aripiprazole versus placebo for antipsychotic-induced hyperprolactinemia published 2013 by Li *et al.* [70]. They evaluated all studies published between January 2001 and December 2012 and five randomized controlled trials [19, 26, 27, 71, 72] with a total of 639 patients (326 adjunctive aripiprazole, 313 adjunctive placebo) met the inclusion criteria. Results showed that adjunctive aripiprazole was generally safe and well tolerated, with no significant increase in the risk of adverse events and discontinuation compared with placebo. Adjunctive aripiprazole was superior to placebo in prolactin level normalization and the appropriate dose of adjunctive aripiprazole was 5 mg/day.

4. Ongoing Clinical Trials

To date, there is only one ongoing study (the DAAMSEL clinical trial, Dopamine partial Agonist, Aripiprazole, for the

Table 1. Risk of Antipsychotic-Induced Hyperprolactinemia (This may be Roughly Explained by their Potency as Dopamine D2 Receptor Antagonists).

Conventional Antipsychotics	+++
Risperidone	+++
Amisulpiride	+++
Paliperidone	++
Olanzapine	++ (more frequent at higher dosages)
Ziprasidone	+ (sometime transient)
Quetiapine	+/- (sometime transient, higher dosages)
Clozapine	+/-
Asenapine	?/-
Aripiprazole	-/↓

Table 2. Published Studies that have been Found in Literature from 2010 since August 2013 concerning Aripiprazole Add-On or Switch to Treat Antipsychotic-Induced Hyperprolactinemia among Psychiatric Patients.

Published Studies with References from 2010 to August 2013	First Antipsychotic	Dosage	Switch or Add-on	Study Design	Weeks	Number of Patients	Results	Comments
Kuloglu *et al.* 2010 [64]	Zuclopenthixole/Risperidone	20-25 mg/day	Switch	Case series	8	5	Effective	Approximately 4 weeks after switch to ariprazole, serum prolactin levels were normalized and all patients reported improvement in their galactorrhea and amenorrhea
Chen *et al.* 2010 [41]	Risperidone/Benzamides	5-20 mg/day	Add-on	Open label	8	24	Effective	Significantly improvement of the Positive and Negative Symptoms Scale (PANSS) score. More efficacy in risperidone than in benzamides
Yasui-Furukori *et al.* 2010 [42]	Risperidone	3-12 mg/die	Add-on	Open label	4	16	Effective	Efficacy also at low dosages (3-6 mg/day)
Ishitobi *et al.* 2010 [40]	Blonanserin	6 mg/day	Add-on	Case report	2	1	Reduction of prolactin levels	
van Kooten *et al.* 2010 [43]	Risperidone long-acting injections (RLAI)	10 mg/day	Add-on	Open label	16	21	Effective	Twelve patients completed the study and were predominantly men, of white origin, with a long duration of illness, and an average of 3.6 years of RLAI treatment

Table (2) contd…..

Published Studies with References from 2010 to August 2013	First Antipsychotic	Dosage	Switch or Add-on	Study Design	Weeks	Number of Patients	Results	Comments
Hill *et al.* 2011 [37]	Zuclopenthixol decanoate 500 mg/RLAI 50 mg	10 mg/day	Add-on	Case series	4/16	2	Effective	First case report on aripiprazole addon in adolescent forensic secure hospital
Wix-Ramos *et al*. [66]	Haloperidol, carbamazepine and levomepromazine	30 mg/day	Switch	Case report	10	1	Reduction of prolactin levels	The patient suffered from pituitary microadenoma with mammary hypertrophy
Broekhof *et al.* 2012 [65]	Risperidone	30 mg/day (plus quinagolide 75 μg)	Switch	Case report	24	1	Reduction of prolactin levels	The patient suffered of macroprolactinoma and psychosis
Ishitobi *et al.* 2012 [67]	Risperidone	2-4 mg/day	Switch	Open label, naturalistic	14.9 ± 8.4 (mean)	3	Effective	The three subjects with hyperprolactinemia were affected by autism spectrum disorders
Anandarajan *et al.* [38]	Risperidone long-acting injections (RLAI)	10 mg/day	Add-on	Case report	8	1	Reduction of prolactin levels	
Basterreche *et al.* [39]	Paliperidone	5 mg/day	Add-on	Case report	4	1	Reduction of prolactin levels	
Trives *et al.* [44]	Risperidone long-acting injections (RLAI)	5 mg/day	Add-on	Open label, naturalistic	12	13	Effective	Twelve of the 13 patients showed a decrease in serum prolactin levels, whereas in two patients, prolactin levels normalized
Lee *et al.* 2013 [46]	Risperidone	10 mg/day vs placebo	Add-on	Randomized controlled trial (RCT)	24	35	Effective	Aripiprazole significantly reduced mean baseline serum prolactin levels within 1 week

Management of Symptomatic ELevated prolactin) [73]. This is a 16-week, double blind, placebo controlled randomized trial of flexible doses of aripiprazole or placebo added to an existing stabilized regimen of prolactin elevating antipsychotics (risperidone, paliperidone, haloperidol, fluphenazine, perphenazine, loxapine) in 50 women with schizophrenia or schizoaffective disorder. However, the results have not been published yet.

5. Mechanism of Action for Aripiprazole in Counteracting the Antipsychotic-Induced Hyperprolactinemia

Aripiprazole has the higher affinity to the dopamine receptor among all available antipsychotics [74].

As a contrast to antipsychotic drugs, which are "pure" dopamine D2 receptor antagonists (that is, without partial agonist properties), aripiprazole may act as a specific modulator of dopamine tone in several regions of the brain and pathways involved in the ethiopathogenesis of schizophrenia, particularly affecting the meso-limbic and the meso-cortical pathways [75]. In fact, aripiprazole may reduce the high "basal" dopaminergic tone, which acts as an antagonist, in regions with reserves of low dopamine D2 receptor and increase the low "basal" dopaminergic tone, which acts as an agonist, in regions with higher reserves of dopamine D2 receptor [73,76]. The latter may explain the effects of aripiprazole in regions with reserves in higher functional receptors, such as the pituitary gland, while counteracting the D2 antagonism induced by antip-

sychotic drugs associated with the hyperprolactinemic effects [77-79]. This positive effect on the levels of prolactin may be observed when aripiprazole is added to another ongoing antipsychotic treatment as well as when drugs are switched.

RECENT PATENS ON HYPERPROLACTINEMIA AND ARIPIPRAZOLE

Some important patents on diagnosis and treatment of hyperprolactinemia and aripiprazole are highlighted below.

1. Somatostatin type-5 receptor agonists have been found effective for treating hyperprolactinemia [80].
2. The co-administration of an effective amount of a growth hormone releasing compound and growth hormone releasing hexapeptide has been found effective for treating hyperprolactinemia [81].
3. Pharmaceutical formulations comprising aripiprazole have been found effective for treating irritability associated with schizophrenia, bipolar disorder, major depression and ASDs [82].
4. A controlled release sterile injectable aripiprazole formulation has been patented for treatment of schizophrenia [83].

CURRENT & FUTURE DEVELOPMENTS

From 2010, when we published in this journal our review on the effect of aripiprazole on antipsychotic-induced hyperprolactinemia [22], the literature has grown up and more robust evidences are present. The more recent studies reviewed showed that the antipsychotic-induced hyperprolactinemia could be partially or totally reversed after adding aripirazole to current treatment or definitely switching to it.

As it has been demonstrated that patient at first psychotic episode who are drug-naïve may have higher prolactin levels than normal controls [84, 85], prolactin levels must be evaluated in all patients before and during treatment with all antipsychotics, with particular attention reserved to known prolactin-raising antipsychotics (Table **1**). Taken together all findings (Table **2**), it is possible to suggest two options to treat with aripiprazole the antipsychotic-induced hyperprolactinemia: 1). The safest strategy may require the addition of aripiprazole to ongoing treatments, in the case patients had previously responded to antipsychotic drugs and then developed hyperprolactinemia. In this instance, it may be possible to also use low doses of aripirazole. However, it is advisable to monitor the patients in case relapses and/or side effect, although rare, might occur 2) Switching drugs should be considered when a patient does not appear to be responding to the previous antipsychotic, thus developing hyperprolactinemia. A cross-taper switch should always be considered, but the risk of a relapse in the disorder may occur more frequently and the patients should be closely monitored. A further and distinct issue is the screening and the management of patients with pituitary disorders and psychotic symptoms and also in this regard aripiprazole would be a useful tool in the psychiatrists armamentarium [66, 86-88].

However, the current available data are still limited. In fact, considering the results of the present review, it is worthy to note that the majority of the published data are case reports or open label studies conducted on a narrow number of patients and, from 2010, only one RCT has been published with encouraging results [46] and another one is ongoing [73]. Even if also a meta-analysis was published with positive results, however more randomized, placebo-controlled studies are still needed to definitely elucidate the role of aripiprazole in antipsychotic-induced hyperprolactinemia.

CONFLICT OF INTEREST

The authors have no potential conflict of interest that is directly relevant to the contents of the manuscript. No pharmaceutical companies were informed of or were involved in the review.

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ABBREVIATIONS

ASDs	=	Autism spectrum disorders
BPRS	=	Brief Psychiatric Rating Scale
DAAMSEL	=	Dopamine partial Agonist, Aripiprazole, for the Management of Symptomatic ELevated prolactin
EPS	=	Extrapyramidal side effects
FDA	=	Food and Drug Administration
PANSS	=	Positive and Negative Symptoms Scale
RCT	=	Randomized controlled trial
RLAI	=	Risperidone long-acting injections

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