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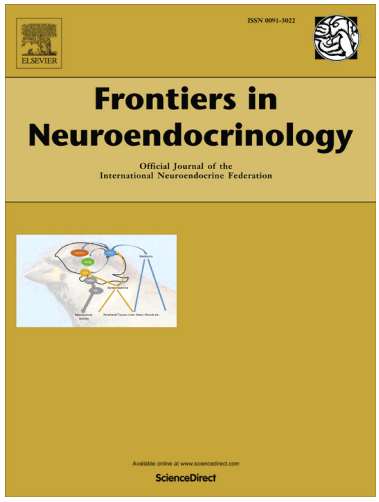

Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics

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Title: Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics

Short title: Antipsychotic-induced hyperprolactinemia

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Abstract

Hyperprolactinemia is an underappreciated/unknown adverse effects of antipyschotics. The consequences of hyperprolactinemia compromise therapeutic adherence and can be serious. We present the consensus recommendations made by a group of experts regarding the management of antipsychotic-induced hyperprolactinemia. The current consensus was developed in 3 phases: 1, review of the scientific literature; 2, subsequent round table discussion to attempt to reach a consensus among the experts; and 3, review by all of the authors of the final conclusions until reaching a complete consensus. We include recommendations on the appropriate time to act after hyperprolactinemia detection and discuss the evidence on available options: decreasing the dose of the antipsychotic drug, switching antipsychotics, adding aripiprazole, adding dopaminergic agonists, and other type of treatment. The consensus also included recommendations for some specific populations such as patients with a first psychotic episode and the pediatric-youth population, bipolar disorder, personality disorders and the elderly population.

Key words

Antipsychotic, neuroleptic, physical health, hyperprolactinemia, consensus

Highlights

- Hyperprolactinemia is an underappreciated adverse-effects of antipsychotics (APS).
- Hyperprolactinemia consequences compromise treatment adherence and can be serious
- We recommend routine determination of the prolactin levels of patients receiving APS.
- Treatment strategies include dose reduction, switching APS, or adding an antidote.

Introduction

There is growing interest in the physical health of patients with mental disorders (Giner et al. 2014; Bobes et al. 2008; De Hert et al. 2010). Given the widespread use of antipsychotics (APS) in psychiatric clinical practice, the high frequency of hyperprolactinemia in patients receiving these drugs and their potential consequences, an important aspect of the physical health of patients under antipsychotic treatment is the recognition and management of hyperprolactinemia associated with the use of antipsychotics. Hyperprolactinemia is a condition in which a person has a level of prolactin above the upper limit of normal range, providing serum sample was obtained without excessive venipuncture stress (Melmed et al. 2011); in most laboratories, the upper limit for prolactin serum concentrations is set at 20 ng/ml for men and 24–25 ng/ml for women (Kelly et al. 2013).

Antipsychotics are usually classified into first-generation or typical antipsychotics (Chlorpromazine, Droperidol, Fluphenazine, Haloperidol, Loxapine, Perphenazine, Pimozide, Prochlorperazine, Thioridazine, Thiothixene, Trifluoperazine) and second-generation or atypical antipsychotics (Amisulpride, Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone). The frequency of hyperprolactinemia in patients who receive antipsychotics varies among studies but can reach 90% in women and 70% in men (Bushe et al. 2008). The frequency of hyperprolactinemia is greater with the first-generation antipsychotics , amisulpride, risperidone and paliperidone, and is lower with aripiprazole and clozapine, with olanzapine and quetiapine occupying a middle ground (Holt and Peueler, 2011). Antipsychotic-related hyperprolactinemia is produced by D2 dopamine receptor blockage, which causes loss of the dopaminergic prolactin inhibitory factor in the lactotroph cells in the anterior pituitary. This explains why APS with a greater D2 occupation index produce higher and more frequent prolactin elevations (Chwieduk and Keating, 2010). This is the case of risperidone (Kinon et al. 2003) and its 9-hydroxymetabolite, paliperidone, that cause hyperprolactinemia most often (Bellantuono and Santone 2012). Another factor involved is their ability to cross the blood-brain barrier: risperidone and paliperidone remain the longest outside of the barrier because of their low liposolubility acting for a longer period in the tuberoinfundibular pathway, provoking hyperprolactinemia (Besnard et al. 2014).

Aripiprazol is a dopamine D2 partial agonist so it rarely provokes hyperprolactinemia (Deanna et al. 2013).

The clinical repercussions of hyperprolactinemia include short-term effects, such as amenorrhea, galactorrhea, gynecomastia and sexual dysfunction, and long-term effects, such as osteoporosis, prolactinoma, increased cardiovascular risk and the development of certain tumors (Bostwick et al. 2009; Cookson et al. 2012). Hyperprolactinemia appears within 72 hours after the initiation of antipsychotic treatment (Meltzer et al, 1976). Serum prolactin levels tend to remain elevated during the length of APS treatment (Igarashi et al. 1985). There are important differences between APS and the relationship between the concentration of APS in brain and plasma (B/P ratio) using PET, which seems to be a biomarker for hyperprolactinemia; the B/P ratio is lower for risperidone and sulpiride than for olanzapine and haloperidol. (Arakawa et al. 2010), Hyperprolactinemia is more frequent in women in naive patients and does not seem to be associated with age or with the severity of the symptoms. (Riecher-Rössler et al. 2013).A group of experts in psychiatry, internal medicine, endocrinology and oncology met to conduct a review of the literature and to form a consensus on the scale of the hyperprolactinemia problem secondary to antipsychotic use (i.e., frequency and clinical repercussions) and to establish recommendations on its detection and management. The results of the analysis of the frequency of the problem and recommendations for its detection have been published elsewhere (Montejo et al. 2016). In this work, we present the recommendations made by that group with respect to the management of hyperprolactinemia associated with the use of antipsychotics.

Materials and methods

The current consensus was developed in 3 phases: 1, review of the scientific literature; 2, subsequent round table discussion to attempt to reach a consensus among the experts that took place in Madrid (Spain); and 3, review by all of the authors of the final conclusions until reaching a complete consensus. The final result has been agreed upon by all of the experts, who reached an agreement by the 4th draft of the manuscript. The entire process took place between March 2014 and March 2015.

1) Review of the scientific literature

An extensive review of the scientific literature was conducted to determine the available published evidence on hyperprolactinemia associated with APS as well as its causes, prevalence and clinical consequences, in addition to issues related to its detection and therapeutic strategies.

A literature search of the PubMed and Cochrane databases was performed using the terms "prolactin" and "antipsychotic" or "hyperprolactinemia" in the title and abstract, in English language and with no limit on the year of publication. This search provided 3,341 articles that were narrowed to 267 after filtering for content relevance. This first part focused on clinical risks and detection of HPRL in 179 articles.

2) Consensus roundtable

A group of 18 experts in Psychiatry (15), Endocrinology (1), Internal Medicine (1) and Oncology (1) chosen by the consensus coordinator (ALM) and from different areas of Spain and with varying academic, research and clinical fields met in person in Madrid in two sessions, morning and afternoon. The consensus was sponsored by the Spanish Association of Sexuality and Mental Health (AESexSAME) and the scientific patronage of the Spanish Society of Biological Psychiatry. The logistic sponsor did not intervene in any of the scientific parts of the consensus or in the preparation of this manuscript.

Each of the experts was previously responsible for the review of the bibliography complied in relation to their area of clinical and research expertise, preparing a communication with the most relevant conclusions that were presented successively at the in-person roundtable discussion of the consensus conference held in Madrid on March 2014. After the in-person discussion session, the review and refinement of the conclusions were completed through electronic communications until reaching unanimous approval. For the presentation of results, levels of evidence and recommendations from the US Agency for Health Research and Quality were taken as a reference. Subsequently, a discussion was set based on the evidence presented by each speaker to reach a consensus on the evidence and the final content to be reflected in this article. The coordinator prepared a preliminary manuscript that was reviewed by all members of the consensus, who sent their comments by email. Four consecutive reviews of the manuscript were necessary to reach overall consensus during the year 2014-2015. Conclusions were agreed upon by 100% of the signatories of the consensus.

Results

General Recommendations:

The general recommendation of the Endocrine Society (Melmed et al. 2011) and Spanish Society of Endocrinology (SEEN) (Halperin et al. 2013) for all cases of hyperprolactinemia secondary to drugs is that the use of dopaminergic agonists is highly controversial given the risk of exacerbating psychotic symptoms and the fact that dopaminergic agonists normalize prolactin in only 75% of cases. If the drug responsible for hyperprolactinemia cannot be withdrawn, the experts recommend substitutive treatment with estrogens/estrogens-progestogens and testosterone in women and men, respectively, with symptomatic hypogonadism and/or decreased bone mineral density.

It is important to determine the appropriate time to act after hyperprolactinemia detection. The intensity of elevated serum prolactin and its clinical repercussions in each individual case determine the need to act on the prescribed APS treatment; additionally, other factors, such as the existence of previous problems of efficacy and/or tolerability of other APS, should be considered.

a) In patients with personal risk factors or a family history of breast cancer and/or osteoporosis, the risk of the use of APS associated with hyperprolactinemia should be considered (Grade D recommendation).

b) For a patient with mild and asymptomatic hyperprolactinemia (<50 ng/mL) with absence of sexual dysfunction, watchful waiting is recommended, conducting regular checks of serum prolactin with at least yearly frequency (Grade D recommendation).

c) In cases of moderate-severe hyperprolactinemia (>50 ng/mL), with clinical repercussions and/or prolonged hyperprolactinemia over time, differential evaluation and diagnosis from a specialized service is recommended (Grade D recommendation). Once assured of the drug-induced origin of the alteration, its pharmacological treatment should be considered. It is important to consider the limited evidence concerning treatment to date and the difficulty in determining with certainty whether findings regarding the treatment of hyperprolactinemia are definitively correlated with improvement of the symptoms to which they are

attributed, such as sexual dysfunction. Different treatment strategies have been described (Montejo and Rico-Villademoros, 2008; Montejo et al. 2010a; Montejo et al. 2005; Kelly et al. 2013; Peveler et al. 2008; Carvalo and Góis, 2011; Nunes et al. 2012) with differing levels of evidence and recommendation that include the following:

1-. Decreasing the dose of the antipsychotic drug
2.- Switching antipsychotics
3.- Adding aripiprazole
4.- Adding dopaminergic agonists
5.- Another type of treatment

A summary of the recommendations for managing antipsychotic-induced hyperprolactinemia is presented in Figure 1

[Figure 1 here]

STRATEGY 1. DECREASING THE DOSE OF THE ANTIPSYCHOTIC

(LE: IV, grade D recommendation)

This is a priori the simplest strategy but is not without risk of relapse (Haddad and Wieck, 2004). Furthermore, the efficacy of this strategy may be questionable, as some APS produce hyperprolactinemia even at very low doses; in other APS, the increase in prolactin appears to be dose-independent, such as the case of amisulpride (Juruena et al. 2010). In the Guide of the Endocrinology Society for the Management of hyperprolactinemia, a specific recommendation is made to be cautious about withdrawing the offending APS drug (Melmed et al. 2011). This strategy may make more sense in those cases in which the APS cause of hyperprolactinemia is effective at lower doses; the safety of decreasing the dose in each individual case will depend on the diagnosis, clinical evolution and pattern of drug treatment.

STRATEGY 2. CHANGING THE ANTIPSYCHOTIC DRUG

(LE: Ib-III, Grade A-C recommendation)

There are data that support a grade C recommendation for the strategy of switching from a high-risk antipsychotic (amisulpride, risperidone, paliperidone or first-generation APS) to a lower risk antipsychotic (aripiprazole, quetiapine, olanzapine or ziprasidone). It is necessary to determine in such cases whether the patient had been previously treated with the alternative drug of choice and whether it was effective in controlling psychotic symptoms and/or was well-tolerated by the patient. Available studies provide variable tests concerning the risk of relapses and improvement of symptoms related to hyperprolactinemia when this strategy is used (Kelly et al. 2013). However, when switching from high doses of antipsychotics, the administration of aripiprazole could provoke abrupt psychotic worsening, especially in patients with dopamine supersensitive psychosis (Takase et al 2015). The safest strategy is that of gradual and overlapping change (Grande et al. 2014) (LE: III).

Several successful studies have been published concerning changing to aripiprazole (LE: III), most of which reported that prolactin levels were reduced significantly (Byerly et al. 2009; Lu et al. 2008; Montejo et al. 2010b; Chen et al. 2011; Mir et al. 2008); 3 studies were undertaken in both sexes (Byerly et al. 2009; Montejo et al. 2010b; Mir et al. 2008), one in females (Lu et al. 2008) and one in males (Chen et al. 2011). In only one study was a greater risk of relapses observed (Kuloglu et al. 2010).

Studies involving changing to olanzapine have reported beneficial effects both in the reduction of PRL and the associated clinical symptoms in both sexes (LE: Ib-III) (Kim et al. 2002; Kaneda et al. 2004; Kinon et al. 2006; Lin et al. 2006).

With respect to switching to quetiapine, a randomized double-blind study examined the relationship between prolactin levels and sexual dysfunction in 22 men. Both prolactin levels and sexual dysfunction were more elevated in the group treated with risperidone than in male patients who switched to quetiapine (LE: IIa, Grade B recommendation) (Nakonezny et al. 2007). Other studies found improvements in sexual dysfunction in both males and females when the sexual dysfunction was controlled by concomitant medication, such as serotonergic antidepressants, hormones or beta-blockers (Montejo et al. 2005), or no improvement (Byerly et al. 2007). Another series of open studies reported normalization of hyperprolactinemia after changing to quetiapine from risperidone (LE: III-IV) in male (Byerly et al. 2004) and female patients (Pardal et al. 2010; Nakajima et al. 2005).

In two open studies undertaken in both sexes, the positive effects of switching to ziprasidone were studied (LE: IV) (Montejo and Rico-Villademoros, 2008; Weiden et al. 2003). Only one study has reported improvement with a switching to clozapine in hyperprolactinemia (LE: Ib); however, clozapine should be reserved for those patients with treatment-resistant schizophrenia (Breier et al. 1999).

With respect to more recently approved APS (asenapine, paliperidone, iloperidone, etc.), there have been no switching studies in patients with hyperprolactinemia that allow the establishment of any type of recommendation in this regard.

It should be noted that while prolactin levels tend to normalize a few days after stopping the causal treatment of hyperprolactinemia, in cases of prolonged exposure, the normalization of prolactin levels can be delayed for weeks or even months in the case of longer duration APS (Haddad and Wieck, 2004). Prolactin levels tend to normalize some days after antipsychotic discontinuation (Montejo 2008). However, with long-acting injectable APS prolactin levels could remain elevated for several months after discontinuation of APS treatment; unfortunately, there is lack of specific information on this regard which it is especially important with risperidone and paliperidone.

STRATEGY 3. ADDITION OF ARIPIPRAZOLE

(LE: Ia, Grade A recommendation)

This is the strategy for which a larger and more robust number of studies has been published, with several double-blind, randomized controlled trials conducted in both sexes (Kane et al. 2009; Shim et al. 2007; Chen et al. 2009), a meta-analysis including patients of either sex (Li et al. 2013) and numerous open studies with Depot (Boggs et al. 2013; Van Kooten et al. 2011) and conventional drugs that include risperidone (Yasui-Furukori et al. 2010; Chen et al. 2010) paliperidone (Roch et al. 2010) and others (Ishitobi et al. 2010).

In a recent meta-analysis of 5 randomized controlled studies with placebo that included a total of 639 patients (326 with aripiprazole, 313 in the placebo group) of either sex (Li et al. 2013), the addition of aripiprazole at a dose of only 5 mg/day was associated with a 79% normalization rate of PRL levels; however, efficacy has been described with various doses in female patients (Yasui-Furukori et al. 2010). Positive results were published in the case of patients of either sex treated with Depot Risperidone (Ziadi

Trives et al. 2013) with aripiprazole dose of 5 mg/day. For some authors, the addition of aripiprazole may represent a safer strategy than switching APS for those patients who have responded to the causal antipsychotic of HPRL (De Berardis et al. 2014); however, there are no comparative studies in this regard. Additionally, it should be noted that polypharmacy increase the risk of certain side-effects such as extrapyramidal symptoms, diabetes or antispsychotic-induced metabolic syndrome (Citrome et al. 2004; Correll et al. 2007; Paton et al 2003).

STRATEGY 4: ADDITION OF DOPAMINERGIC AGONISTS

(LE: Ib, Grade B recommendation)

Most recent publications refer to the use of bromocriptine and cabergoline, although the use of amantadine or terguride, a partial dopaminergic agonist, has been described for this purpose (Hashimoto et al. 2014). A systematic review conducted in 2011 that included patients of either sex concludes that the use of cabergoline is preferable to bromocriptine with respect to efficacy and safety (Dos Santos et al. 2011).

A randomized, controlled study reported efficacy and tolerability with bromocriptine in female patients (Lee et al. 2010). Other studies with a lower grade of evidence, generally case series with small samples, have also reported efficacy and safety of bromocriptine and cabergoline in either sex (García-Rico et al. 2012; Barszcz et al. 2008; Cavallaro et al. 2004; Tollin, 2000), even in young patients of either sex (mean age: 23.3±0.5 years) (Pollice et al. 2007) and male children (Cohen and Biederman, 2001).

However, the addition of dopaminergic agonists is a controversial strategy (Peveler et al. 2008), as some data suggest that it can aggravate psychosis (Chang et al. 2008), increase hallucinations and aggressiveness (Hashimoto et al. 2014) or cause the appearance of abnormal involuntary movements (Yvan et al. 2008) and even cardiopulmonary complications (Rack et al. 2004; Andersohn et al. 2009).

According to recommendations by SEEN (Alperin et al. 2013), *"this option should only be considered, under strict control, in cases in which the antipsychotic drug cannot be substituted and there is absolute contraindication of substitutive treatment with estrogens/testosterone, or in the special circumstance of women that, within this context, desire gestation".*

Hence, despite the evidence, this strategy is recommended in cases in which the previous strategies have not been possible or effective; more randomized clinical trials are needed to determine the efficacy and safety of this method in this group of patients.

STRATEGY 5. ANOTHER TYPE OF TREATMENT

In Asian countries, studies have been conducted on the effectiveness of certain types of preparations based on medicinal herbs, with good efficacy results and safety, as is the case of Peony-Glycyrrhiza Decoction in female patients (Yuan et al. 2008) or Shakuyaku-kanzo-to in patients of either sex (Yamada et al. 1997) in the treatment of hyperprolactinemia associated with APS use (LE: III, Grade C recommendation).

If it is not possible to change the treatment, the specific treatment of symptoms associated with hyperprolactinemia, such as hypogonadism, sexual dysfunction and repercussions on the bone system, may be appropriate.

- Use of estrogens or testosterone in patients with prolonged hypogonadism and/or decreased bone mineral density (Melmed et al. 2011; Halperin et al. 2013).
- Use of phosphodiesterase inhibitors for the treatment of erectile dysfunction associated with HPRL (Gopalakrishnan et al. 2006; Aviv et al. 2004; Mitsonis et al 2008).
- Attempting to curtail risk factors of osteoporosis by promoting a healthy diet and regular physical exercise and by avoiding, whenever possible, tobacco and alcohol consumption (Grade C recommendation), although in psychotic patients, this goal is not easy to achieve.
- In the case of amenorrhea maintained more than 6 months, if it is not possible to change treatment, the use of oral contraceptives is recommended to prevent osteoporosis (Peveler et al. 2008).
- When insufficient levels of vitamin D are detected, supplementation with 800-1000 IU/day of vitamin D is recommended (Grade B recommendation)
- In patients with problems following a diet rich in calcium (4-5 daily serving of dairy products, equivalent to 1 L of milk), supplementation with

pharmacological calcium (500-1000 mg/day) is recommended (Grade B recommendation).

- When the risk of fracture is considered to be very high, pharmacological treatment of osteoporosis should be commenced.

Recommendations in some special groups

FIRST PSYCHOTIC EPISODES AND THE PEDIATRIC-YOUTH POPULATION

In patients with a first psychotic episode, it is very likely that the initiated APS treatment must be maintained for many years with the consequent commitment to safety. However, it is well-established that the younger (<18 years of age) population is at an increased risk of experiencing adverse effects in the short- (<6 months) and medium-term (6-12 months), such as sedation, extrapyramidalism, weight gain, dyslipidemia and adverse effects related to prolactin (Correl CU, 2006; Merchán-Naranjo et al. 2012), with an emphasis on the long-term (>12 months) effects of hyperprolactinemia, such as deleterious effects on bone. The latter could impede reaching peak bone mass, the maximum of which is reached at approximately 25 years, with the resulting future risk of osteoporosis and fracture (Colao et al. 2003; Takahashi et al. 2013).

In a cross-sectional study involving 83 male children or adolescents treated with risperidone, a decrease in volumetric bone mineral density in the ultradistal zone of the radius and lumbar was observed (Calarge et al. 2010). After adjusting for age, sexual maturity, height and body mass index, serum prolactin was found to be inversely correlated with bone mass ($P < 0.03$). Sexual side effects can also intensely affect younger patients of either sex, possibly leading to decreased adherence to medication (Byerly et al. 2007).

In a review on the safety data of APS in the pediatric population, a risk profile of hyperprolactinemia has been established in the following order, from higher to lower risk: paliperidone/risperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole (Ben Amor, 2012). Other systematic reviews of the use of APS in the youth population of either sex report an increased risk of hyperprolactinemia with

risperidone versus placebo and olanzapine, and with olanzapine vs placebo and a lower risk of aripiprazole vs placebo (LE: Ia-II) (Seida et al. 2012; Almandil, 2013) or vs active comparatoors (Fraguas et al. 2011). In a review of the pediatric population of either sex exposed to APS, frequency of hyperprolactinemia ranged between 50-91% for patients treated with risperidone and 90% for haloperidol (Rosenbloom Al, 2010). In a cross-sectional study of young male and female patients exposed to APS (Laita et al. 2007), hyperprolactinemia was detected in 48.5% of patients with more than a year of treatment, with a significant correlation observed between prolactin levels and the group treated with risperidone (p=0.021). The relevance of this problem in the pediatric-youth population has been subject to thorough study, and these results have been recently confirmed by a meta-analysis (Druyts et al. 2014) (LE: Ia).

We are waiting for pharmacogenetic strategies that can help us evaluate the long-term risks of some of the adverse effects of drugs in carriers of the DRD2*A1 allele (Young et al. 2004) and the knowledge of the true gene-environment interaction (Bernardo et al. 2013). Until then, when treating the pediatric population and first psychotic episodes (more common in the youth population), it is especially important to evaluate the tolerability profile of the drugs we use; it is advised that the clinic act according to consensuses on physical health that relates to patients with severe mental disorders (Sainz Ruiz et al. 2008; Bobes et al. 2008; Mané and Bernardo, 2005).

BIPOLAR DISORDER

Hyperprolactinemia is a common adverse effect in patients of either sex with bipolar disorder (BD), given the elevated frequency of APS use, especially in the manic and maintenance phases (Vieta et al. 2013a). The new definition of mixed episodes from DSM-5 can favor even greater use of antipsychotics (Vieta and Valentí, 2013b; de Dios et al. 2014). Unfortunately, there is little published data on the bipolar population, although the available evidence suggests that hyperprolactinemia associated with APS in BD is lower than in schizophrenia (LE: IIb) (Bushe et al. 2010). The population group in which there is more substantiated information is in children and adolescents. In a review study of double-blind, placebo-controlled clinical trials that included patients of either sex conducted in Spain, it was shown that greater rates of hyperprolactinemia occur with risperidone (N=571), with increases from 8.3 to 49.6 ng/ml (Fraguas et al.

2011). In other randomized clinical trials conducted in children and adolescents of either sex, an average dose of 2.57 mg/day of risperidone was associated with an average increase in prolactin from 7.2 to 44.8 ng/ml after 8 weeks of treatment (Geller et al. 2012). In another study conducted with olanzapine in adolescents of either sex, an11 ng/ml increase in hyperprolactinemia was produced in 47% of patients (Kryzhanovskaya et al. 2009).

In bipolar disorder, in addition to APS, another type of drug is usually used, such as a mood stabilizer or antidepressant. In the case of mood stabilizers, there are data to indicate that valproate does not seem to affect PRL levels in male patients (Aldemir et al. 2012) and that lithium may even have a lowering effect on PRL levels both in female (El Khoury et al. 2003) and male (Bastürk et al. 2001) patients (LE: IIb). With respect to antidepressants, there are more than 40 hyperprolactinemia reports in patients treated with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, although there is only one ad hoc study in the case of fluoxetine (which was associated with hyperprolactinemia in 12.5% of patients of the study, 4.5% of male patients and 22.2% of female patients) (Papakostas, 2006) and sertraline, with negative results in female patients (Sagud et al. 2002) (LE: III).

For the hyperprolactinemia approach in bipolar patients, the recommendations of screening, follow-up and treatment are largely the same as those generally described for hyperprolactinemia from APS. However, with respect to the strategy of changing the APS, it is especially important to consider potential interactions of the drug chosen for the switching and its polarity index – e.g., its ability to prevent manic versus depressive relapses, which can vary considerably from drug to drug (Grade D recommendation) (Grande et al. 2014; Bernardo et al. 2011; Popovic et al. 2012).

PERSONALITY DISORDERS

The use of APS is a phenomenon generalized in the treatment of personality disorders. Specifically, the efficacy of APS has been confirmed in more than twenty controlled clinical trials with placebo in the treatment of borderline personality disorder (BPD) (Vita et al. 2011).

Adherence to the treatment of these patients is very low, partly motivated by the poor tolerance to the potential adverse effects (Carrasco et al. 2012). Thus, there is importance in considering a number of characteristics that could explain increased susceptibility to adverse effects associated with HPRL, such as higher prevalence in women of childbearing age, patterns of intense and often uncontrolled sexual activity, and special intolerance to somatic symptoms, as is apparent in solid epidemiological studies in personality disorders (Coid , 2013; Ansell et al. 2007).

However, the available evidence of hyperprolactinemia repercussions in this population group is very low. Only one double-blind study of olanzapine vs placebo in men and women with BPD reported a significant increase in prolactin levels and related symptoms in 27.5% of the subjects treated with olanzapine compared with 12.1% treated with placebo (Schulz et al. 2008). Several case series of patients of either sex have also been published in which 40%-70% of patients exhibited abnormally high prolactin levels after regular treatment with risperidone (Carrasco et al. 2012).

ELDERLY POPULATION

The use of APS is common in elderly people (i.e. ≥65 years), particularly in the institutionalized population (Alexopoulos et al. 2004). A general characteristic of mental diseases in the elderly is the more frequent appearance of psychotic symptoms relative to younger adults (for example, in cases of depression, bipolar disorder, delirium, schizophrenia or dementia, among others) (Skoog I., 2011). Another common risk is their greater sensitivity to some of the adverse effects of APS, such as extrapyramidal symptoms, cardiovascular symptoms and those associated with hyperprolactinemia (Rado and Janicak, 2012). Older patients tend to accumulate risk factors for some of the adverse effects associated with hyperprolactinemia, such as sexual dysfunction, osteoporosis and the associated risk of bone fracture, with associated consequent functional loss and immobility syndrome (Kinon et al. 2003b; Graham et al. 2011). Furthermore, it is likely that in elderly men and women with psychotic disorders, adverse effects are present with lower levels of prolactin than in younger subjects (Weizman et al. 1983; Bai et al. 2002). In addition, there may be a cumulative effect between different causes of hyperprolactinemia, such as the presence of hepatic or renal dysfunction and the use of other drugs that increase prolactin (opioid

analgesics, some antihypertensives, metoclopramide or domperidone) (Valdés Socin et al. 2002; Holt , 2008).

Hyperprolactinemia detection can be more difficult in older patients, especially in women, in whom the post-menopausal stage prevents the use of amenorrhea as a sentinel symptom. The effects on sex life are also easily masked, given the decreased activity and sexual desire conditioned by other factors (Rubio-Aurioles and Bivalacqua, 2013). The same can be said about osteoporosis and other clinical consequences. Thus, hyperprolactinemia in this population may be particularly harmful.

Conclusions

Hyperprolactinemia is one of the underappreciated/unknown adverse effects of APS. The short-, medium- and long-term consequences of HPRL compromise therapeutic adherence and can be serious.

1. Prolactin is increased after the administration of certain APS; the drugs that produce the highest levels of PRL include the typical APS, such as amisulpride, paliperidone and risperidone, and those that are less associated with increases include clozapine, quetiapine and aripiprazole (which even lowers previous prolactin levels).

2. It is necessary to inform patients of the effects associated with hyperprolactinemia when it is detected and to decide together the best strategy for maintaining efficacy and preserving safety and adherence.

3. Mild hyperprolactinemia levels between 25 and 50 ng/ml should be monitored periodically and, in the case of amenorrhea >3 months, a change in APS must be assessed for the risk of osteoporosis.

4. Prolactin levels greater than 50 ng/ml and/or associated with clinical repercussions (including systematic exploration of possible sexual dysfunction) require a treatment intervention, such as decreased dosage, change of APS or the addition of drugs with demonstrated ability to reduce prolactin levels (aripiprazole).

5. Hyperprolactinemia is considered severe when it is > 100 ng/ml (present in >30% of patients with risperidone or paliperidone) and must always be addressed even when there is no amenorrhea-galactorrhea because of the medium/long-term risk of osteoporosis, cardiovascular issues and possible breast or endometrial cancer risk increased. Prolactinoma should be ruled out but, unfortunately, typically goes unnoticed because of a lack of attention or detection by prescribers.

6. When treating a set of often silent and rare side effects reported spontaneously by patients, systematic, routine and continuous determination of the prolactin levels of patients with APS treatment is recommended.

7. Treatment options for hyperprolactinemia may be considered depending on the type of side effect detected, its impact on the patient, and careful weighing of the pros and cons of continuing with the current medication or starting a new therapeutic strategy.

8. Different treatment strategies have been described with differing levels of evidence and recommendation that include the following: decreasing the dose of the antipsychotic drug, switching antipsychotic, adding aripiprazole or adding dopaminergic agonists including pros and cons in each one. Selecting a personalized strategy for each patient is the best strategy.

9. We need a new intervention model to preserve safety, quality of life and adherence to treatment. The model must consider the comprehensive assessment of chronic and often silent side effects associated with the use of APS, which are often not expressed spontaneously by the patient or underestimated by the prescriber but nonetheless compromise quality of life, adherence and safety of the patient.

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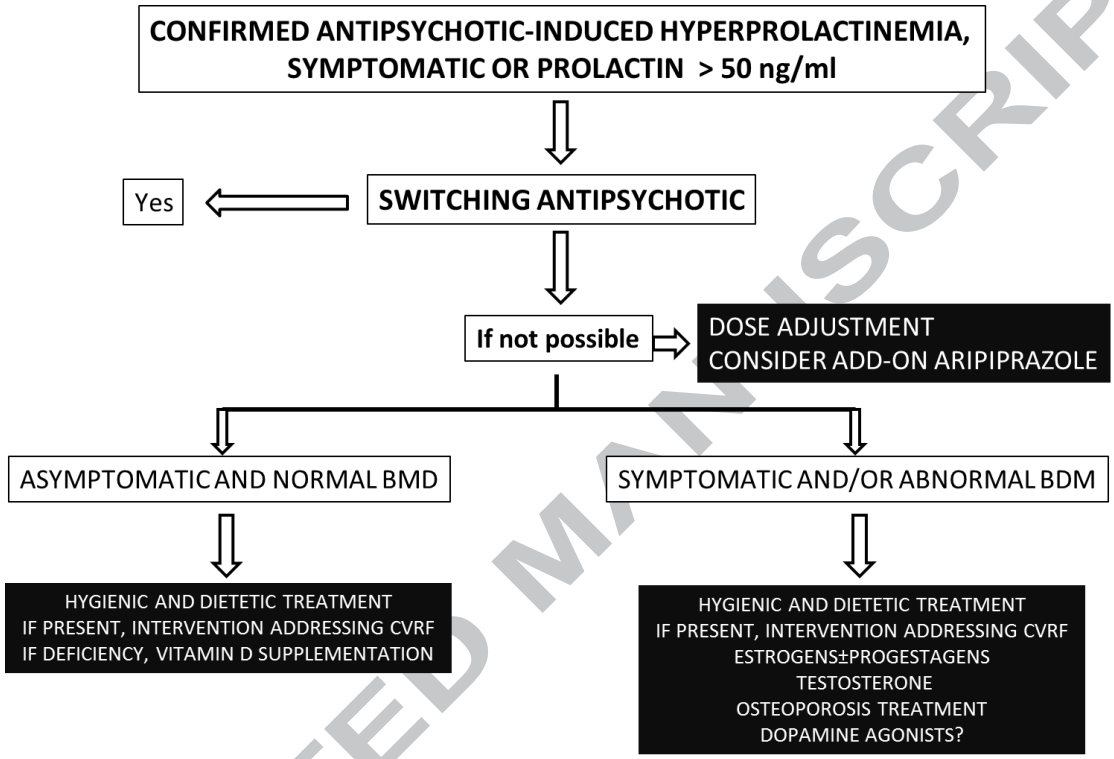
Figure 1

Proposed algorithm for the management of antipsychotic-induced hyperprolactinemia



Highlights

- Hyperprolactinemia is an underappreciated adverse-effects of antipsychotics (APS).
- Hyperprolactinemia consequences compromise treatment adherence and can be serious
- We recommend routine determination of the prolactin levels of patients receiving APS.
- Treatment strategies include dose reduction, switching APS, or adding an antidote.