LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

# Danish Pharmacovigilance Update

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## In this issue



## New study on hormonal contraception and depression

In September, the article "Association of Hormonal Contraception With Depression" (Skovlund CW, Mørch ST, Kessing LV, Lidegaard Ø) was published in the Jama Psychiatry journal. The article describes a Danish registry study seeking to demonstrate the association between use of various types of hormonal contraception and the established adverse reaction of depression in an observational study. The results of the study have been addressed in several Danish and foreign media, the focus being depression as an adverse reaction to hormonal contraception.

### The registry study in brief

The study observes women aged 15-32 years in the period from 2000-2013 in the Danish registries, focusing on prescriptions redeemed for hormonal contraception as well as first prescriptions redeemed for antidepressants or first hospital admissions with depression as the diagnosis at discharge. Women who had previously redeemed a prescription for an antidepressant and women with a prior diagnosis of depression were excluded. Altogether 1,061,997 women were observed (avg. 6.4 years). The women left the study temporarily during pregnancy and maternity periods (due to the risk of post-natal depression).

The authors compare women taking hormonal contraception with non-users.

In summary, the study shows that

- the risk of depression among women using hormonal contraception is slightly higher for those using contraceptive vaginal rings and patches compared to those taking contraceptive pills,
- antidepressants are apparently being prescribed to treat the adverse reaction of depression.

The relative risk of prescription for an antidepressant depending on product type (adjusted analysis, primary regression analysis) is as follows:

- Combination products:
  Contraceptive patches (2.0 [95% CI, 1.76-2.18]) and contraceptive vaginal rings (1.6 [1.55-1.69]) carry a higher risk overall than contraceptive pills (1.2 [1.22-1.25].
- Progestin products:
  Hormonal intrauterine devices (1.4 [1.31-1.42]) carry about the same risk as mini pills (1.3 [1.18-1.37][1] and 1.4 [1.30-1.46][2].

A similar pattern is observed for admissions for depression.

**Time and age aspects (subgroup analyses):**
The risk of prescriptions for antidepressants and admissions for depression was highest among the 15 to 19-year-olds and peaked after six months of treatment.

**Be aware that depression is a known adverse reaction to hormonal contraception**
Since depression is a known and common adverse reaction to hormonal contraception, the study provides no new knowledge as such. However, it is worth noting that the risk of depression is seemingly higher for contraceptive vaginal rings and patches compared to contraceptive pills. The authors offer the higher dose as an explanation, but perhaps the finding can also be ascribed to the fact that contraceptive patches and vaginal rings are popular among those who find it difficult to take a pill every day, i.e. a specifically vulnerable group.

The study moreover shows that doctors prescribe antidepressants to treat the common adverse reaction of sadness/depression in users of hormonal contraception – perhaps without first having adjusted the hormonal contraception treatment. This practice gives cause for concern; partly because an adverse reaction to medical treatment should generally not be treated with another medicine; and partly because antidepressants can have many (and serious) adverse reactions.

Depression, sadness and mood swings appear as common adverse reactions in the summaries of product characteristics and package leaflets for the individual hormonal contraceptive products – albeit in various terms.

**The DKMA encourages doctors to**

- pay attention to depression as an adverse reaction in users of hormonal contraceptives,
- discuss the risk associated with using hormonal contraceptives with girls/women about to start treatment.

## Intense itching and/or urticaria after discontinuation of the antihistamine Zyrtec (cetirizine) added as a new adverse reaction to the medicine's product information

In August 2016, the product information of the antihistamine Zyrtec was added itching and/or urticaria after discontinuation to the list of adverse reactions. The adverse reaction may occur even if these symptoms are not present before initiation of treatment; in some cases the symptoms may be so strong that it becomes necessary to resume treatment.

[1] Norethisterone
[2] Desogestrel

### Why the adverse reaction is added to the product information

441 cases of withdrawal syndrome or rebound effect after discontinuation of cetirizine have been reported to the company marketing Zyrtec. In the vast majority of cases, the users experienced intense and often universal itching and some also developed urticaria. 74 of the cases were reported by a doctor or other healthcare professional, the rest by users.

The DKMA has received five ADR reports from users aged from 10 to 52 years. The ADR reports describe that the skin reactions typically commence 1-2 days after discontinuation of the medicine. The symptoms are described as different from and worse than the conditions the medicine was supposed to treat, e.g. allergic rhinitis. Some patients were able to taper off the medicine over weeks or months, but many had to resume treatment because of the severe skin reactions.

### Possible mechanisms

The aetiology of the phenomenon is unknown. It cannot be excluded that it is an altered translation of the initial allergic reaction, but it does not explain why specifically skin reactions, and not allergic rhinitis for example, are reported. Nor is there any explanation why the reaction is much stronger than the allergy's initial symptoms or why some patients actually succeed in tapering off the medicine.

It is also possible that it is a withdrawal reaction. This is consistent with the symptoms presenting at a time after medicine discontinuation when the skin may start reacting to histamine again. Discontinuation reactions are known to occur for opioids, benzodiazepines and SSRIs, etc. Withdrawal reactions are described for other medicines as well, e.g. malignant neuroleptic syndrome after sudden discontinuation of dopamine agonists or tramadol and convulsions, etc. after discontinuation of pregabalin (e.g. Lyrica).

### Report the adverse reaction to the DKMA

Regardless of the mechanism, there is limited knowledge about the phenomenon. For example, we do not know if other antihistamines could cause similar reactions or how to help the affected patients. We therefore encourage doctors not only to report the adverse reaction, but to publish case reports as well.

### Antihistamine consumption on the rise in Denmark

Antihistamine consumption is increasing moderately in Denmark. Overall, the consumption of antihistamines grew from approx. 59 million daily doses in 2011 to 71 million daily doses in 2015. At 33 million daily doses in 2015, cetirizine is the most sold antihistamine in Denmark (source: Medstat).

### Other cetirizine-containing products

Please be aware that not all cetirizine package leaflets will be updated with the new adverse reaction at first. This is because Zyrtec accounts for only a very small share of cetirizine products sold in Denmark. Other cetirizine-containing medicines that are not updated with the adverse reaction include Alnok, Benaday, Vialerg and Cetirizin "Actavis". Since the ADR reports submitted in Denmark concern the products Alnok, Benaday as well as Cetirizin"Actavis", it is considered likely that the adverse reaction is relevant for them too.

## Neurological, metabolic and psychiatric adverse reactions in children and adolescents treated with aripiprazole

The antipsychotic aripiprazole is authorised for treatment of schizophrenia in adults and adolescents from the age of 15 and for treatment of manic episodes in adolescents aged 13 years and over.

Despite this, a report shows that several children in Denmark younger than 15 and 13 are treated with aripiprazole (figures 1 and 2). The highest consumption is, however, still recorded for the age groups 15-19, which are comprised by the authorised indications for aripiprazole products.

Together with a group of psychiatrists, the DKMA has reviewed ADR reports of neurological, psychiatric and metabolic adverse reactions in children and adolescents who are treated with aripiprazole.

The review of the ADR reports is published in the article *Neurological, Metabolic, and Psychiatric Adverse Events in Children and Adolescents Treated With Aripiprazole* in the Clinical Psychopharmacology journal (ref: KD Jacobsen et al. 2016)

A summary of the results of the review is provided below:

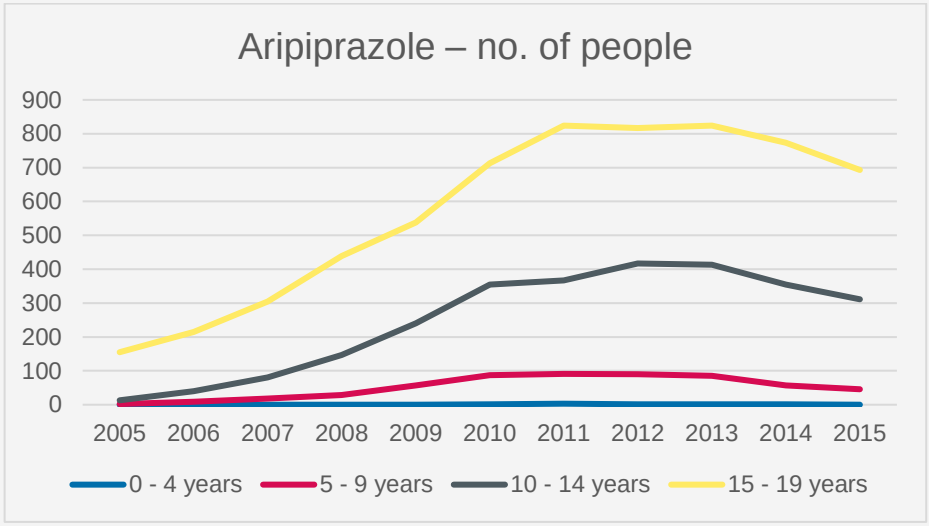


Figure 1: Number of children and adolescents having redeemed at least one prescription for aripiprazole from 2005 to 2015 (medstat.dk).

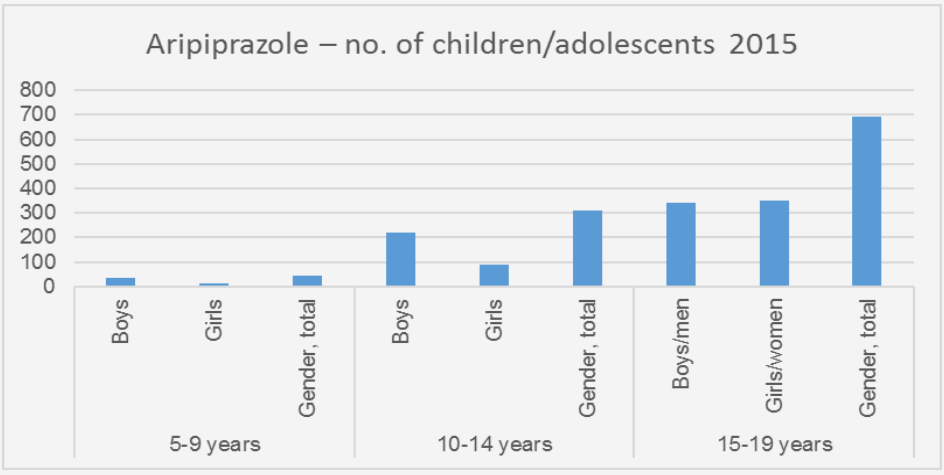


Figure 2: Number of children and adolescents having redeemed at least one prescription for aripiprazole by gender and age group in 2015 (medstat.dk).

As can be seen from figure 2, predominantly boys redeemed a prescription for aripiprazole in 2015 – note, however, that the age group 15-19 is split more or less evenly on boys and girls.

## ADR reports about children and adolescents treated with aripiprazole

The ADR reports[3] are described in tables 1 and 2.

| Case | Year | Gender | Age | Diagnoses (ICD-10) | Adverse reactions* |
|---|---|---|---|---|---|
| **Mental disorders** | | | | | |
| 1. | 2009 | M | 14 | Schizophrenia | Convulsion affecting hands and feet as well as muscle spasms |
| 2. | 2010 | F | 14 | Psychosis | Malignant neuroleptic syndrome |
| 3. | 2011 | M | 17 | Schizophrenia | Hand tremor |
| 4. | 2012 | M | 12 | Psychosis | Anxiety, nightmares and vomiting |
| 5. | 2013 | M | 15 | Schizophrenia | Hypersalivation |
| 6. | 2011 | F | 14 | ASD, epilepsy, OCD and Tourette's syndrome | Chronic insomnia and Parkinson's disease |
| **Non-mental disorders** | | | | | |
| 7. | 2012 | M | 5 | ADHD, specific developmental disorder and brain damage | Fatigue, motor rigidity, tics, binge eating and aggressive behaviour |
| 8. | 2012 | F | 11 | ASD | Orthostatic hypotension, dizziness and balance disturbance |
| 9. | 2013 | F | 11 | ASD, Tourette's syndrome | Hallucinations, tics, suicidal behaviour, weight gain and akathisia |
| 10. | 2013 | M | 17 | ADHD and psychosis | Sedation |
| 11. | 2015 | M | 16 | ADHD, ASD and mental retardation | Dystonia, facial muscle spasms, involuntary movements of arms and legs and throat noises |
| 12. | 2010 | M | 7 | Tourette's syndrome | Mydriasis, blurred and stiff vision |

Table 1. Neurological and psychiatric adverse reactions in children and adolescents treated with aripiprazole
ASD = autism spectrum disorders

| Case | Year | Gender | Age | Diagnoses (ICD-10) | Adverse reactions* |
|---|---|---|---|---|---|
| **Non-mental disorders** | | | | | |
| 13. | 2013 | M | 12 | Anxiety and impaired development | Weight gain (8 kg) and restlessness |
| 14. | 2015 | F | 11 | Incontinence | Hair loss, depression and psychosis |
| 15. | 2010 | F | 10 | ADHD | Weight gain (19 kg) |
| 16. | 2013 | F | 14 | ? | Hypercholesterolemia |
| 17. | 2014 | F | 16 | Anorexia nervosa | Hypercholesterolemia |
| 18. | 2014 | M | 15 | Unknown | Weight gain (7 kg) |
| 19. | 2015 | F | 17 | ASD and anorexia nervosa | Weight gain (10 kg) |

Table 2. Metabolic adverse reactions in children and adolescents treated with aripiprazole ASD = autism spectrum disorders. The described adverse reactions are reported suspected adverse reactions for which it is not possible to assess causality with the medicine.

[3] All cases referred to in this article originate from the DKMA's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases the to DKMA.

### Conclusions

The review shows that aripiprazole has been used off label in several cases, including for treatment of Tourette's syndrome and OCD as well as in children and adolescents younger than the authorised age limit.

The review also shows that children with ASD who are treated with aripiprazole may develop serious psychiatric adverse reactions such as severe chronic sleep disorders, aggressive behaviour and hallucinations.

The DKMA encourages doctors to pay attention to these serious adverse reactions in children and adolescents treated with aripiprazole.

## The DKMA has published three reports on the use of melatonin among children and adolescents

The number of melatonin users aged between 0-17 years has grown over the last five years. For this reason, the DKMA decided to review users, adverse reactions and the possible risks of effects on sexual maturation in relation to melatonin use. The analyses are included in the assessment of whether a potential safety problem is associated with melatonin use in children and adolescents.

### Consumption and diagnoses

In the first report, *Melatonin – Users between 0-17 years of melatonin-containing medicines (in Danish only)*, the DKMA has investigated, among other things, if the children and adolescents who were prescribed melatonin in 2015 had a diagnosis covered by the Danish Health Authority's guideline on medical treatment of children and adolescents with psychiatric disorders. 86 per cent of the melatonin users had at least one relevant diagnosis registered in the National Patient Registry and/or had redeemed a prescription for other relevant medication.

Moreover, the report looks at the ADR reports received by the DKMA. There are four serious ADR reports about melatonin-containing medicines involving children and adolescents between 0-17 years. However, for these reports, it has been considered less likely that there is a link to melatonin use. None of the ADR reports shift the benefit-risk balance, and the reporting pattern gives no immediate cause for concern. No signals or other safety issues involving melatonin have been raised in the DKMA's European network.

The report is available here: *Melatonin – users between 0-17 years of melatonin-containing medicines (in Danish only)*.

### Effects on sexual maturation

In the second report, *Melatonin – possible unintended effect on sexual maturation – a literature study (in Danish only),* the DKMA reviews the literature on possible unintended effects on sexual maturation. The conclusion is that numerous animal trials are inconsistent when it comes to melatonin's effect on sexual maturation. Some studies have shown accelerated sexual maturation, others absent or delayed sexual maturation. Based on the animal trials conducted, it is not possible to clarify if there is a risk of impacts on puberty in children.

The report is available here: *Melatonin – possible unintended effect on sexual maturation – a literature study (in Danish only).*

### Adverse reactions in children and adolescents receiving melatonin

The third report reviews the scientific literature on adverse reactions to melatonin-containing medicines in children and adolescents. The report concludes that melatonin treatment has mild and usually transient adverse reactions when used in

children and adolescents. However, no studies have systematically investigated if the adverse reactions are related to the duration of treatment. Among the common adverse reactions are headache, dizziness, nausea and sleepiness. There are no published reports of very severe or life-threatening adverse reactions.

The report is available here: *Melatonin: Adverse reactions in children and adolescents – a literature study (in Danish only)*



## EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed on the PRAC meeting in September 2016 concern the following products:

- **Agomelatine** – urinary retention
- **Directly-acting antivirals (DAAV)** – drug interaction between DAAV and vitamin K antagonists leading to a reduced INR (international normalised ratio)
- **Cobicistat-containing medicines** – drug interaction with corticosteroids leading to adrenal suppression
- **Iomeprol** – haemolysis

See EU's list of recommendations on safety signals: *PRAC recommendations on signals September 2016* as well as the *Danish translations of the product information from September 2016*.

## Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Tiotropium 10 microgram, inhalation powder, hard capsules (Braltus) in COPD maintenance treatment:** Minimisation of the risk of medication errors. Sent out September 2016.
- **Antineoplastic antibody blinatumomab (Blincyto):** Risk of pancreatitis. Sent out October 2016.

The DHPCs are available at the DKMA website – most of them in Danish only: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

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