Danish Pharmacovigilance Update # 3

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Restrictions on the use of codeine for cough and cold in children

The European Pharmacovigilance Risk Assessment Committee (PRAC) has concluded a review of the benefits and risks of using codeine for cough and cold in children due to concerns about the risk of serious respiratory depression caused by opioid toxicity. In 2013, the committee reviewed the risk profile of codeine when used for pain relief in children.

In this current review, the PRAC concluded that the use of codeine for cough and cold in children should be restricted. The PRAC considered that the risk of opioid toxicity is particularly high in children because of the variable and unpredictable way codeine is converted into morphine in children and because cough and cold in children are often self-limiting conditions. Furthermore, evidence indicates that the effect of codeine in treating cough and cold is limited in children.

Recommendations for codeine use in children

In relation to the treatment of cough, the summary of product characteristics recommends the following:

- Codeine is contraindicated for treatment of cough in children below 12 years.
- Codeine should not be used for cough and cold in children and adolescents between 12 and 18 years who have problems with breathing.

In addition, the contraindications resulting from the review in 2013 still apply:

- Codeine is contraindicated in all patients known to be CYP2D6 ultra-rapid metabolisers irrespective of age.
- Codeine is contraindicated in breastfeeding women because morphine is excreted in breast milk.

Codeine is converted to morphine in the liver by the CYP2D6 enzyme. Variations in CYP2D6 could limit or completely inhibit the effect of codeine (slow metabolisers, estimated to account for 7 % per cent of the population) or could increase the risk of opioid toxicity due to higher morphine concentrations (ultra-rapid metabolisers – the incidence rate of which varies between populations). Some of the children who experienced severe adverse reactions were CYP2D6 ultra-rapid metabolisers.

Read the previous article about restrictions on the use of codeine in children *Danish Pharmacovigilance Update, August 2013.*

News from the EU

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[1].

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 February 2015 concern the following products:

- **Amiodarone** – SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- **Aripiprazole** – Hyperprolactinaemia

See EU's list of recommendations on safety signals: *PRAC recommendations on signals.*

[1]The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Quetiapine and ADR reports of deaths

As part of the DHMA's pharmacovigilance activities, we have recently focused on antipsychotics. In particular, an increase in patients being treated with the antipsychotic quetiapine has caught our attention.

Since 2004, we have received a total of 30 ADR reports that describe deaths suspected as adverse reactions to quetiapine. Based on our review of the cause of death and co-medication in these ADR reports, prescribers are reminded of the importance to comply with the current guidelines in the area.

Review of the 30 reported deaths related to quetiapine treatment

Age and gender distribution of the 30 patients who died while being treated with quetiapine:

- ADR reports with undisclosed age and gender (8)
- Foetus with malformation (1)
- 49-year-old (gender unknown) (1)
- 45-year-old (gender unknown) (1)
- Nine women aged 33-69 years (33, 36, 48, 49, 50, 69 years) (three with age unknown)
- Ten men aged 19-78 years (19, 22, 27, 30, 34, 57, 70, 78 years) (two with age unknown)

Reported cause of death in the 30 patients

Cause of death	Number
Cardiac arrest	4
Pulmonary embolism possibly caused by deep vein thrombosis	5
Cause of death unknown (several of the patients died suddenly)	7
Cardiovascular disturbances (with previous, known heart disease)	1
Aortic rupture	1
Drug intoxication (suicide not suspected)	3
Shock and multi-organ failure*	1
Diabetic ketoacidosis (possible undiagnosed diabetes)	1
Volvulus	1
Suicide	4
Foetus with malformations – abortion	1
Aspiration pneumonia (patient was retarded with reduced reflexes)	1

*Male in his 20s who developed acute pancreatitis with diabetic ketoacidosis and extreme hypertriglyceridemia >55 mmol/l

All cases referred to in this article originate from the Danish Health and Medicines Authority'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 to the Danish Health and Medicines Authority.

Indications reported for quetiapine use in the 30 patients:

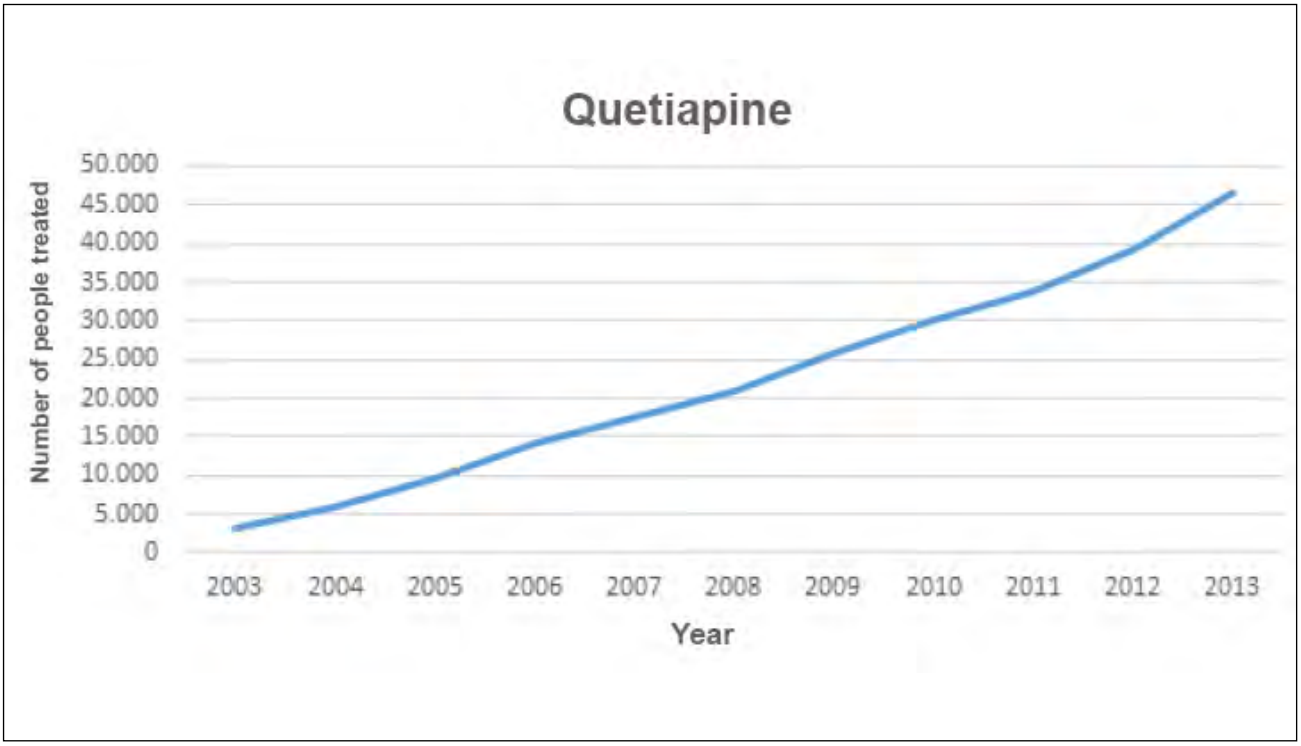
- Reports with indication unknown (11)
- Schizophrenia (6)
- Bipolar disorder (3)
- Psychotic (2)
- Depression (2)
- Anxiety (2)
- Personality disorder (1)
- ADHD (1)
- Mental disorder (1)
- Restlessness (1)

Co-medication/polypharmacy/treatment with several antipsychotics

21 of the 30 patients who died were treated with several different medicinal products. While 13 of the 21 patients were treated concomitantly with two or more antipsychotics, 11 of the 21 patients were treated concomitantly with a benzodiazepine. In nine of the patients, the ADR reports described no other use of medicines. One of the patients was suspected to have undiagnosed diabetes.

Large increase in the number of quetiapine users

The number of people on quetiapine medication has risen markedly since 2003 – from 3,211 in 2003 to 46,495 in 2013. The DHMA will be investigating possible causes of this increase.



Treatment guidelines

Treatment with antipsychotics is known to cause numerous adverse reactions, including heart rhythm disturbances. Mortality increases when antipsychotics are taken together with sleeping pills and tranquillisers, and polypharmacy increases the risk of adverse reactions.

Danish and international data indicate that the risk of death is higher when several antipsychotics are taken concomitantly. The Danish guideline published by the DHMA 'Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser nr. 9276 af 6. maj 2014' (in Danish only) (Guideline no. 9276 of 6 May 2014 on treatment with antipsychotics in people over 18 years suffering from psychotic disorders) highlights the importance to carefully monitor treatment efficiency and development of possible adverse reactions and avoid the concomitant use of several antipsychotics.

In compliance with the DHMA's latest guideline *"Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser nr. 9276 af 6. maj 2014" (in Danish only)*, **doctors should be aware of the following:**

- Avoid concomitant treatment with antipsychotics and benzodiazepines after the acute phase (1-2 weeks) as treatment increases the risk of death.
- There is no evidence that concomitant treatment with several antipsychotics (polypharmacy) increases efficacy. On the contrary, polypharmacy appears to cause more adverse reactions.
- Generally, high doses of 1st generation drugs should not be used in the treatment of psychotic disorders due to the risk of cardiovascular and anticholinergic effects.

The patient should be monitored at the start of treatment and after 2, 4, 8, and 12 weeks; In long-term treatment, at least once a year.

Prescribers should ensure monitoring, etc. of the following:

- Height and weight measurement
- BMI calculation
- Waist measurement
- Blood pressure measurement
- Hba1c and lipid measurements
- ECG monitoring

After each monitoring, the doctor treating the patient must decide on the continued medical treatment.

The Danish Society of Cardiology and the Danish Psychiatric Society have developed an algorithm that is to reduce the risk of cardiac arrhythmia and sudden death induced by psychoactive drugs *"Arytmi-risiko ved anvendelse af psykofarmaka' (in Danish only).*

Indication for quetiapine
Quetiapine is an atypical antipsychotic (2nd generation) agent used in the treatment of:

- Schizophrenia and other psychotic conditions characterised by emotional changes, thought disorders, hallucinations and delusions, possibly psychomotor restlessness and excitation.
- Treatment of moderate to severe manic episodes and moderate to severe depressive episodes in bipolar disorder.
- Prevention of manic or depressive episodes in patients with bipolar disorders who have previously responded to quetiapine treatment.
- As adjunctive treatment of depressive episodes in unipolar depression when monotherapy with an antidepressant did not prove sufficient.

Tetracyclines and raised intracranial pressure

In January, the DHMA received an ADR report about a patient in his/her early thirties who, for a couple of months, had been treated with tetracyclines for acne.

A few weeks after the treatment started, the patient developed persistent mild headache. Approx. six weeks later, the patient also developed a sensation of pressure on the eyes. The medicine was discontinued, and the patient was immediately referred to a specialist who diagnosed the patient with bilateral papilledema and intracranial pressure.

By the time the ADR report was submitted, the patient was recovering.

The DHMA has received altogether 10 ADR reports that describe patients having developed raised intracranial pressure as a suspected adverse reaction to tetracycline treatment. In the summary of product characteristics, intracranial pressure is described as a rare adverse reaction (≥1/10,000 to <1/1,000).

Doctors should be aware of the following:

- Bulging fontanelles in infants as well as benign intracranial hypertension in adults have been reported as adverse reactions during treatment with tetracyclines.
- Treatment should cease if there are signs of raised intracranial pressure.
- The condition reverses quickly when treatment is discontinued.

Indication for tetracyclines
Infections caused by bacteria sensitive to tetracyclines. Unless strictly indicated, tetracyclines should not be used in children younger than 12 years of age.

All cases referred to in this article originate from the Danish Health and Medicines Authority'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 to the Danish Health and Medicines Authority.

Childhood vaccinations and reported suspected adverse reactions in Q4 of 2014

Every three months, the reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme are reviewed and assessed by the DHMA and a vaccination panel composed of a number of internal and external experts in Denmark. Here are the results of the review for Q4 2014.

Since adverse reactions to the HPV vaccine have generated a lot of attention in the last couple of years, we continue to split our review on two sections:

1. A review of the ADR reports related to vaccines in the childhood immunisation programme – excluding the HPV vaccine.

2. A review of the ADR reports related to the HPV vaccine.

The review covers the primary vaccines in the childhood immunisation programme as well as the booster vaccines (re-vaccination).

Reports of adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine) Q4 of 2014

In the fourth quarter of 2014, the DHMA received a total of 88 ADR reports about vaccines in the childhood immunisation programme (excluding the HPV vaccine). 15 of them were classified as serious[1].

Vaccine	Serious	Non-serious	Total
DT booster	0	2	2
DTaP-IPV Booster	0	1	1
DTaP-IPV Booster / DTaP-IPV/Act-Hib	0	1	1
DTaP-IPV Booster / DTaP-IPV/Act-Hib / Prevenar 13	0	1	1
DTaP-IPV /Act-Hib	6	12	18
DTaP-IPV /Act-Hib / Prevenar 13	2	15	17
Infanrix Hexa	2	11	13
Infanrix Hexa / Prevenar 13	1	5	6
MMR Vaxpro	0	5	5
Pneumovax	0	1	1
Prevenar 13	2	2	4
Priorix	0	2	2
DTaP Booster[2]	0	8	8
DTaP Booster / IPV[2]	1	2	3
IPV[2]	0	5	5
IPV / Hepatitis A and B[2]	1	0	1
Total	15	73	88

Table 1a. Reports broken down by severity

[1] A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

[2] The reports were received throughout 2014, but are included in the fourth quarter of 2014 for practical reasons.

Review and assessment of the serious reports

When we assess the serious ADR reports, we investigate whether it is likely that there is a causal connection to the vaccine.

The result of our causality assessment is split into three categories[3]:

- Possible
- Less likely
- Not possible to assess

Vaccine	ADR description	Assessment and causality
DTaP-IPV, Act-Hib, Prevenar 13 (Engerix B)	A 5-month-old girl developed infantile spasms about 14 days after the last vaccine dose.	Infantile spasms occur before the age of 12 months. A study from 2012[4] found no increased incidence of epilepsy after vaccination with DTaP-IPV Act-Hib. Causality is therefore considered **less likely.**
DTaP-IPV, Act-Hib, Prevenar 13	A 4-month-old baby developed asthmatic bronchitis about one month after vaccination.	Asthmatic bronchitis is a very common disorder, occurring often in the first 12 months. There is no evidence of causality in the literature, and causality is therefore considered as **less likely**
DTaP-IPV, Act-Hib	A 1-year-old child developed vaccination granuloma and asthmatic bronchitis within the same year she was vaccinated.	The formation of granuloma is a known adverse reaction, and causality is therefore considered **possible.** It is considered **less likely,** that there is a connection between the vaccine and asthmatic bronchitis as the condition is very common. The literature provides no evidence of causality.
DTaP-IPV, Act-Hib	A 23-month-old boy developed pertussis. He had received all vaccine doses.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.
Infanrix Hexa	A 5-month-old boy developed an abscess about three months after vaccination. The abscess was located at the injection site, which had been swollen since the vaccination.	In every intramuscular injection, there is a risk of abscess formation. Thus, it is a case of vaccine failure.
DTaP-IPV, Act-Hib	A 17-month-old girl developed pertussis. The girl had received all vaccine doses.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.
DTaP-IPV, Act-Hib	An 18-month-old girl developed pertussis. The girl had received all vaccine doses.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.
DTaP-IPV/Act-Hib	A 3-year-old girl developed pertussis. The girl had received all vaccine doses.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.
Infanrix Hexa, Prevenar13	A 4-month-old girl had seizures and fever the day after vaccination.	Fever and febrile seizures are known adverse reactions, and causality is therefore considered **possible.**
Prevanar 13	A 3-year-old fully vaccinated girl was by blood cultures diagnosed with invasive type 1 pneumococcal infection.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.
Prevanar 13	A 4-year-old fully vaccinated girl was by blood cultures diagnosed with invasive type 1 pneumococcal infection.	It is known that the vaccine does not offer full protection. Thus, it is a case of vaccine failure.

Table 1b: Description of the suspected adverse reactions described in the serious ADR reports and subsequent causality assessment.

[3]We will apply the new classification of causality assessment for ADR reports that we described in *Danish Pharmacovigilance Update, January 2015* in our next review of reported suspected adverse reactions in the childhood immunisation programme Q1 2015.

[4]Sun Y et al: Risk of febrile seizures and epilepsy after vaccination with diphteria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus type B, JAMA 2012;307(8):823-831.

Infanrix Hexa	A few hours after vaccination, a 1-year-old boy developed skin changes on lower extremity resembling Arthus reaction type III, hypersensitivity. The skin changes were near the injection site.	This is a rare, but known, hypersensitivity reaction to especially the tetanus component. Causality is therefore considedered **possible.**
DTaP-IPV Act-Hib	Literature report[5]. A 7-month-old girl developed pyoderma gangrenosum at the injection site about 14 days after vaccination. One month later, she developed changes resembling Sweet's syndrome. She was treated with steroid, azathioprine and lastly with Infliximab at good effect.	There is a close temporal relationship between the vaccination and pyoderma gangrenosum at the injection site. A description of this complication has not been found elsewhere. Due to he close temporal relationship, causality is considered **possible.**
DTaP Booster, IPV	After vaccination, a 5-year-old child developed extensive swelling and redness on the one thigh and was sent to hospital for observation for a short period.	The symptoms were interpreted as an irritation or allergic condition. These are known adverse reactions to the vaccines, and causality is considered **possible.**
IPV, Twinrix (Hepatitis A and B)	An adult man developed Guillain-Barré syndrome about 2-3 weeks after vaccination.	There is a close temporal relationship. Guillain-Barré syndrome is mentioned in the summary of product characteristics as a possible adverse reaction to the hepatitis vaccines and a connection to Twinrix is considered **possible.**

Table 1b: Description of the suspected adverse reactions described in the serious ADR reports and subsequent causality assessment.

Six ADR reports described vaccine failure of the vaccine in question. Neither vaccine failure nor the lack of efficacy of a medicinal product falls within the definition of adverse reactions, but is included in the overall safety monitoring activities. Since no vaccine offers 100 % effectiveness, disease cases will appear after vaccination. The number of cases in a vaccinated population primarily depends on the frequency of the disease in the background population.

Review of the non-serious ADR reports

73 reports were classified as non-serious.

Among the non-serious suspected adverse reactions were the formation of granuloma (15%), metal allergy (13%) as well as general reactions to the vaccine (20%) the most common reactions. These are known adverse reactions to the vaccines that are described in their summaries of product characteristics.

The reported non-serious adverse drug reactions included one report that described the development of atopic eczema as a suspected adverse reaction to the MMR, Vaxpro-vaccine.

Conclusion

In the fourth quarter of 2014, we received a total of 88 ADR reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine).

15 were classified as serious, which is almost the same as previously. In the majority of these reports, it was assessed that a causal connection to the vaccine was possible.

None of the new data shift the benefit-risk balance, and the DHMA assesses that the benefits of the vaccines still outweigh the possible risks.

[5]Mahler B. et al. Effect of infliximab in sweet's syndrome-pyoderma gangraenosum overlap syndrome. Pediatric Rheumatology. 2014;12:SUPPL.1

ADR reports about the HPV vaccine received in Q4 2014

In the fourth quarter of 2014, the DHMA received a total of 69 ADR reports about the HPV vaccine. 39 were classified as serious.

Table 2a shows the number of ADR reports classified as serious and non-serious.

Vaccine	Serious	Non-serious	Total
HPV vaccine	39	30	69

Table 2a. Reports broken down by severity.

Number of doses sold and number of ADR reports from 2009-2014

HPV vaccine	2009	2010	2011	2012	2013	2014	Total
Number of reports	288	66	43	96	511	224	1228
Number of serious reports	25	5	6	18	177	91	322
Number of doses sold	347,690	151,476	163,374	349,730	488,224	114,457	1,614,951

Table 2: The total number of ADR reports related to the HPV vaccine received from 2009 to 31 December 2014 and the number of reports classified as serious. The number of HPV vaccine doses sold in Denmark is also shown. (Please be aware that when the DHMA receives additional information, this may imply changes. Consequently, there may be small variations between previously published figures and the above figures.)

Age distribution

The HPV vaccine is the only vaccine included in the Danish childhood immunisation programme that is also offered free of charge to women outside the childhood programme.

From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts. Since 1 January 2014, the HPV vaccine has been offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer is available until the end of 2015.

Table 2c shows the age distribution of the girls/women described in the ADR reports we received in the fourth quarter.

Number of ADR reports about persons under 18	Number of ADR reports about persons aged 18 or over	Number of ADR reports with age unknown
30	36	3

Table 2c. Age of the girls/women for whom adverse reactions have been reported.

Review and assessment of the serious reports about the HPV vaccine

ADR description	Assessment and causality
A patient developed narcolepsy/cataplexy about 17 months after vaccination	There is no temporal relationship between the symptoms and the vaccination, and it is not a known adverse reaction. Causality is therefore considered **less likely.**
Arm pain, ulnar nerve entrapment and headache, etc. previous fracture, now progressive symptoms and muscle atrophy.	It is **not possible to assess** if there is a possible causal relationship on the available information. The woman was already in agony because of the previous fracture, and whether the described worsening of the condition could be caused by the vaccine cannot be determined.
Neuropathy, paraesthesia	The ADR report contains very little information, which implies it is **not possible to assess** any potential causal link to the vaccine.
Multiple symptoms, among which sinusitis, long-term fatigue and migraine.	It was only possible to confirm the diagnosis of sinusitis with the patient's own doctor, and this condition is considered **less likely** to be connected to the vaccine.
Multiple symptoms, among which headache and dizziness.	Many of the symptoms were present before vaccination according to the patient's own doctor. Thus, there is no temporal relationship between the symptoms and the vaccination. Causality is therefore considered **less likely**.
Multiple symptoms, among which sensory disturbances, tiredness, influenza symptoms, etc.	There is a temporal relationship, but there is too little information about assessment and diagnosis if any. Based on the information available, it is **not possible to assess** any causality.
POTS	There is a temporal relationship between symptom onset and vaccination. Causality is therefore considered **possible**. (Also see the conclusion)
Induced abortion as the foetus had trisomy 13	The risk factor for chromosome abnormalities is primarily the age of the mother. There is no evidence in literature of an association between chromosome abnormalities and vaccinations. Causality is therefore considered **less likely**.
Multiple symptoms, among which rectal bleeding, headache, tiredness, mood swings, etc.	There are numerous symptoms, and the evaluation has led to no diagnosis. For some of the symptoms, e.g. rectal bleeding, causality is considered to be **less likely** based on the available literature. As for the other symptoms, the information available means it is **not possible to assess** causality.
Cataplexy, narcolepsy, etc.	The symptoms occurred about two months after vaccination. There is no evidence in literature of a connection between vaccination and narcolepsy or hypersomnia, and therefore causality is considered **less likely.**
Hypersomnia	The symptoms occurred about one month after vaccination. There is no evidence in the literature of a connection between vaccination and narcolepsy or hypersomnia, and therefore causality is considered **less likely.**
Tiredness, headache, etc.	The patient had intercurrent enterovirus meningitis, which could explain the symptoms, and therefore causality is considered **less likely.**
Multiple symptoms – both psychiatric changes and somatic conditions (110 different conditions)	This is a case of numerous symptoms and no overall diagnosis. Many of the symptoms were present before vaccination. Based on the literature and the summary of product characteristics, it is considered **less likely,** that there is a connection between the vaccine and the symptoms.
Tiredness and muscle weakness	The symptoms developed almost one year after the last vaccine dose. No diagnosis has been made. Due to the time interval it is, despite the limited information, considered **less likely,** that there is a connection.
Multiple symptoms, including tiredness, fits, fainting, etc. – no positive tests yet, but examinations are still ongoing POTS examination is pending.	The patient had multiple symptoms, but no diagnosis, and examinations are still ongoing. Based on the information available, it is therefore **not possible to assess** any causality.
Multiple symptoms, including headache, sensory disturbances, etc. – no diagnosis despite extensive examinations	The symptoms started less than two years after vaccination, and therefore a connection to the vaccine is considered **less likely.**
POTS, autonomic dysfunction	There is a temporal relationship between the symptoms and the vaccine, and causality is therefore considered **possible**. (Also see the conclusion)
POTS, many symptoms	There is a temporal relationship between the symptoms and the vaccine, and causality is therefore considered **possible**. (also see the conclusion)
Multiple complaints, including bladder pain, headache, tiredness, etc.	The symptoms did not occur until about 18 months after the last vaccine dose, and causality is therefore considered **less likely.**
Polyneuropathy, severe fatigue, etc. autonomic dysfunction (not POTS)	Symptom onset after the second dose of Gardasil®. There is a temporal relationship between the symptoms and vaccination, but the patient had no diagnosis. Based on the available information it is **not possible to assess** causality.

Multiple symptoms, migraine, sensory disturbances in right side of the body	Many intercurrent disorders. There is no obvious temporal relationship between the symptoms and the vaccination. Migraine occurred with menstruation. It is considered **less likely** that there should be a connection to the vaccine as other circumstances can explain the symptoms.
Brain haemorrhage	The patient suffered a brain haemorrhage about two months after the last HPV vaccine dose. In the literature, no similar case after vaccination is found, and therefore it is considered **less likely** that the vaccine should be the cause of a brain haemorrhage.
Multiple symptoms, among which memory problems, palpitations, migraine, etc.	The symptoms occurred about 14 days after the first dose of Gardasil®. There is no overall diagnosis of all the symptoms, and therefore it is **not possible to assess** any causal link to the vaccine.
Breathing difficulty, dizziness, joint pain, spontaneous abortion week 20	There is no information about examinations. Based on the available information, it is **not possible to assess** if there is a connection between the vaccine and the patient's symptoms. In the literature, there is no description of an increase in the number of spontaneous abortions after vaccination with Gardasil®, and therefore causality is considered **less likely.**
Tiredness and dizziness	A connection is considered **less likely**, as there is no obvious temporal relationship between the symptoms and the vaccination.
Episodes of dizziness, migraine with aura	The episodes occurred about 18 months after the last vaccine dose, and therefore causality is considered **less likely.**
Muscle and back pain	There is a temporal relationship between the vaccination and the symptoms, but the patient's disorder is common. But since the report contains too litle information, causality is **not possible to assess.**
Vaccinated with both Gardasil® and Priorix® Stomach pain, dizziness and influenza-like episodes	The report includes too little information, and presently, the patient has not been diagnosed conclusively, and therefore it is **not possible to assess** causality.
Pain in the extremities, dizziness, weakness and sensory disturbances. Referred for further examination of immune reactions	The symptoms occurred about six months after vaccination. The symptoms were dizziness and muscle pain, but apart from the note "Referred for further examination of immune reactions", no diagnosis is mentioned. It is therefore **not possible to assess** causality based on the available information.
Chest pain, reduced sensation	The symptoms occurred about two years after vaccination, and causality is therefore considered **less likely**.
Headache	There is too little information. Long-term headache is not a known adverse reaction, but there is a temporal relationship. Since headache is very common and there is no evidence in the literature of long-term headache after vaccination, causality is considered **less likely** .
POTS	The patient developed symptoms of POTS after the first dose of Gardasil®. Causality is considered **possible**. (Also see the conclusion)
Joint pain, tiredness, headache, etc.	The patient developed joint pain, and there is a temporal relationship between these symptoms and the vaccination. In the meantime, no other examination results or medical descriptions have been received, and therefore it is **not possible to assess** any causality. As for the other symptoms, there is no temporal relationship, and therefore causality is considered **less likely.**
Pain, autonomic dysfunction, paresthesia, etc. not POTS	The symptoms occurred after the first dose of Gardasil®, however, based on the available information, it is **not possible to assess** any causality.
POTS with many symptoms	The symptoms occurred some weeks after the first dose of Gardasil®. Causality is considered **possible**. (Also see the conclusion)
Tiredness, sensory disturbances and many other symptoms	No examinations have been made, and on the basis available, it is **not possible to assess** any causality.
Paresthesia, autonomic dysfunction, dyspnoea, etc.	The symptoms occurred in the week after vaccination. Thus, there is a temporal relationship, but no conclusive diagnosis yet. Based on the available information, it is **not possible to assess** any causality.
Stomach pain, headache, dizziness, tiredness, autonomic dysfunction	Although there is a temporal relationship, it is **not possible to assess** any causality based on the available information.
Transverse myelitis, sensory disturbances	Diagnosed four months after the last vaccine dose. Cases of transverse myelitis have been described for several vaccines, and causality is considered **possible.**

Table 2d. Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

The table shows that in the fourth quarter there were five new cases of POTS and a case of transverse myelitis.

When ADR reports describe symptoms occurring one year after the last vaccine dose, causality is generally considered less likely.

Two cases of narcolepsy were reported; In the one case, symptom onset occurred 17 months after vaccination. To this date in Denmark, there are four ADR reports of narcolepsy suspected as an adverse reaction to the HPV vaccine. By comparison 1.6 million doses of the vaccine are distributed every year in Denmark. In Denmark, between 2,500-3,000 people suffer from the disease[6]. There is no evidence in the literature suggesting that the vaccine and narcolepsy are connected.

Review of the non-serious ADR reports

In the 30 non-serious ADR reports on the HPV vaccine, the most common symptoms were headache, tiredness and dizziness (accounting for 9%, 6% and 5% of the adverse reactions). The symptoms in these cases lasted longer than described in the vaccine's summary of product characteristics.

In addition, there were many different symptoms such as nausea and paresthesia.

Conclusion

We received a total of 69 ADR reports concerning the HPV vaccine in the fourth quarter of 2014. 39 of them were classified as serious. This quarter, more than half of the reports concerned women older than 18 years.

It is still debated if the vaccine can cause POTS (Postural Orthostatic Tachycardia Syndrome). The Pharmacovigilance Risk Assessment Committee has concluded that presently it is not possible to confirm or disprove that there is a causal relationship between Gardasil® vaccination and the occurrence of POTS and CRPS (Complex Regional Pain Syndrome). POTS and CRPS should therefore be monitored closely in future reviews of Gardasil® safety[7].

In this review, none of the new data shift the benefit-risk balance, and the DHMA assesses that the benefits of the vaccine still outweigh the possible risks.

Focus remains aimed at suspected adverse reactions to the HPV vaccine

As part of the DHMA's pharmacovigilance activities, we work together with experts to further analyse the Danish reports of suspected adverse reactions to the HPV vaccine. Any conclusions from this analysis will be included in the ongoing European assessment of the HPV vaccine.

[6]Danish Narcolepsy Association (www.dansknarkolepsiforening.dk)
[7]http://sundhedsstyrelsen.dk/en/health/vaccination/hpv-vaccination/adverse-reactions-from-the-hpv-vaccine

All cases referred to in this article originate from the Danish Health and Medicines Authority'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 to the Danish Health and Medicines Authority.

Short news

Newly published article on the safety of paracetamol

A newly published article[1] reviews a number of published studies on the safety of treating adults with paracetamol in recommended doses.

The studies are observational cohort studies that investigate the exposure of paracetamol in standard doses (0.5-1g up to maximum 4g daily) in the general population. The review includes only studies that have investigated the risk of death, cardiovascular, gastrointestinal and renal-related adverse reactions.

In most of the studies, a dose-response was seen for most investigated endpoints, and the authors conclude that data suggest that paracetamol – especially in high doses – could be associated with a considerable degree of toxicity. However, the authors emphasise that the results should be interpreted cautiously since the studies are observational studies some of which are based on self-reporting of medicine consumption and without any control of any concomitant use of other medicines. Further studies are therefore needed to draw any firm conclusions.

The DHMA's opinion

The conclusions of the article should be seen together with other literature and knowledge in the area. As highlighted by the authors, the studies are associated with a number of uncertainties in relation to randomised clinical studies, as e.g. it can be very difficult to distinguish a potential adverse reaction to the medicine from events that may be related to the underlying causes triggering the patient's need for pain-relief.

The DHMA still assesses that paracetamol should be the first choice for pain-relief when medically needed.

[1]Roberts E. et. al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2015 Mar 2. pii: annrheumdis-2014-206914.

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