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Mirtazapine and possible occurrence of:
Amnesia
DRESS

Quick Read

A new causal association has been found between exposure to mirtazapine and both amnesia and DRESS. Either of these reactions requires prompt suspension of treatment. They will both be included in the product information of this antidepressant.

***Mirtazapine**, an antidepressant indicated for the treatment of major depression, is a centrally active, pre-synaptic alpha-2 antagonist that increases noradrenergic and serotoninergic neurotransmission. H1 histamine receptor antagonism further confers sedative properties to this drug.*

***Amnesia** can be caused by brain injury or disease and may be associated with stress, anxiety or depression, but it can also have a pharmacological cause.*

***DRESS** (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a rare (circa 0.4 cases per million people), idiosyncratic, potentially fatal adverse drug reaction. It is clinically characterized by generalized morbilliform skin rash, fever, lymphadenopathy, blood abnormalities and multiorgan involvement (liver, kidneys, lungs, heart, nervous, GI and/or endocrine systems). Its pathophysiology is only partially understood and it is thought to be associated with immunological and/or genetic factors. Though often difficult, early diagnosis of DRESS and discontinuation of the suspected offending drug are paramount for its treatment. Carbamazepine and allopurinol are probably the two drugs most frequently associated with DRESS, but dozens of other medicines have been added to a growing list of potentially involved drugs.*

*Click **here** for a Boletim article on drug-related, serious cutaneous adverse reactions (SCARs) including DRESS.*

A review of cases in the UK and the Netherlands pharmacovigilance databases has detected evidence of occurrence of both amnesia and DRESS in association with products containing mirtazapine. The products' SPCs and PILs did not have sufficient information on those reactions. Following an assessment of all available data, the PRAC at EMA has recommended an update to those documents (see overleaf).

Cont'd overleaf ▶

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Adriana Gamboa, Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Magda Pedro, Márcia Silva, Patrícia Catalão, Sílvia Duarte
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P.
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: farmacovigilancia@infarmed.pt
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▶ *(Cont'd from previous page)*

The reported cases of amnesia that were analyzed in the safety review included, among others, twenty cases in patients younger than 60 years in whom a plausible relation was found with exposure to mirtazapine, as well as improvement or resolution on therapeutic discontinuation. In three cases the memory disorder recurred on resumption of mirtazapine. Likelier plausible clinical explanations have not been found.

A possible mechanism for the occurrence of amnesia / memory disorders with mirtazapine, though based solely on data from pre-clinical studies, could be the drug's antagonistic effect on H1 receptors. Mirtazapine could also affect memory function through stimulation of serotoninergic and noradrenergic neurotransmission.

Update of the SPC of products containing mirtazapine:

4.8. Undesirable effects

Table of ADRs – Nervous system disorders

Frequency 'common': Amnesia*

*In most cases patients recovered after drug withdrawal.

4.4. Special warnings and precautions for use

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme, which can be life-threatening or fatal, have been reported in association with <mirtazapine> treatment.

If signs and symptoms suggestive of these reactions appear, <mirtazapine> should be withdrawn immediately.

If the patient has developed one of these reactions with the use of <mirtazapine>, treatment with <mirtazapine> must not be restarted in this patient at any time.

4.8. Undesirable effects

[...]

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Frequency: not known

Cristina Mousinho

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

ADRs in the literature

COVID-19: safety concerns / adverse effects are main reason for vaccination hesitancy or refusal

Often seen as an essential tool for a more definitive control of the current pandemic, the development of a vaccine for COVID-19 has, for obvious reasons, been the subject of great interest.

Meanwhile, compliance with vaccination during the previous influenza A (H1N1) pandemic was relatively low. The June Editorial of the European Journal of Health Economics reveals an online survey conducted on a total of 7,664 persons corresponding to representative samples from seven European countries (Denmark, France, Germany, Italy, Netherlands, Portugal and United Kingdom) as well as one region that was analyzed separately from its country – Lombardy. The survey looked at the willingness of the subjects to be vaccinated against COVID-19 should a vaccine become available.

Overall, 74% said they wished to be vaccinated. This intention was highest in Denmark and in the United Kingdom (80%) and lowest in France (62%). It was high in Portugal (75%), though 21% of the Portuguese were not sure and five percent expressed the wish not to be vaccinated. In the whole of the countries' sample, this proportion did not differ much: 19% and 7%, respectively.

Again in the sample as a whole, the proportion of males willing to be immunized was significantly higher than that of females (78% vs 70%), especially in men over 55 years of age. In both genders, younger age groups (18-24 years) were the least willing to be vaccinated.

Of the hesitant individuals, not unlike other studies on vaccination hesitancy, a total of 70% pointed to potential vaccine side effects or generic safety concerns as their reason.

Half of the individuals considering refusing vaccination presented the same reasons as the hesitant respondents, while 8% would rather "let nature follow its course", 10% were "against vaccines in general", and 11% thought that COVID-19 was "not a risk for their health".

Some of the concerns frequently expressed by the respondents in free text were: apprehension on account of the vaccine being experimental and of lack of studies on adverse reactions, as well as apprehension that the vaccine may not be safe for specific groups such as pregnant women or persons with background conditions such as multiple sclerosis, allergies, etc.

The authors of this Editorial then go on to discuss strategies to increase vaccination willingness. For this purpose, the following equation is deemed relevant: vaccine adoption = access + acceptance. They further delve into considerations on R0, which reflects the number of people that can be expected to acquire the disease from each single infected individual.

Given that the threshold for group immunity corresponds to the proportion of the population that needs to be immune for disease transmission to become stable (R=1), the higher the value of R0 the higher the group immunity threshold, i.e., the greater the proportion of the population that needs to be immune. With an estimated European R0 of 3.87 in one study, group immunity threshold in Europe could be as high as 74% (total percentage of people that need to be immune, either from having had the virus or from having been vaccinated). However, since individual susceptibility to the virus is probably variable, the proportion of population that needs to become immune could turn out to be lower.

- ***Neumann-Böhme S et al. Once we have it, will we use it? A European survey on willingness to be vaccinated against COVID-19. The European Journal of Health Economics (2020) 21:977–982.***

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Anacinra Kineret	**Physicians:** rheumatologists, internists and paediatricians experienced in diagnosing and treating CAPS (Cryopyrin-Associated Periodic Syndromes), Still's disease and FMF (Familial Mediterranean Fever) **Nurses:** experienced in CAPS, Still's disease and FMF	Brochure for healthcare professionals
	Patients	Brochure for patients / caregivers 27-07-2020
Vedolizumab Entyvio	**Physicians:** gastroenterologists	Important safety information
	Patients	Alert card 13-07-2020

Compiled by Patrícia Catalão

The Portuguese National Pharmacovigilance System is counting on healthcare professionals to keep reporting any ADRs that may occur with medicinal products used in the treatment of COVID-19 – see infographic (in Portuguese)

Portal **RAM**

Notificação de Reações Adversas a Medicamentos

Report an adverse drug reaction here.
Find answers to your questions about the ADR Portal here.