Open Letter VII, to Dr Ian Hudson, Chief Executive of MHRA

31 March 2017

ADHD drugs, MHRA and the Concerta scandal – suicides, suicide attempts and self-harm

Dear Dr Hudson,

I should have come back much earlier, but the secrecy stamps from MHRA and the Swedish Medical Products Agency (MPA) have made it impossible to gain access to the important facts *about suicides, suicide attempts and self-harm in connection with methylphenidate treatment.*

It's first now, four month after your answer (below) that we can compare the data from the pharmaceutical companies with the reliable data from Sweden about suicides, suicide attempts and self-harm, revealed in my investigation.

As you know the manufacturers of methylphenidate (Concerta, Ritalin, Equasym, Medikinet) were ordered by the MHRA and the EMA Pharmacovigilance Risk Assessment Committee (PRAC) to *"undertake a cumulative review of all cases of self-injurious behaviour"* in connection with their products (1). These reviews were to be presented in the next Periodic Safety Update Reports (PSURs), to be submitted to the MHRA/EMA in the end of 2016.

We could thus, in these reports, expect to get *exact data* about *all* cases of self-injurious behaviour (including suicides and suicide attempts) in connection with methylphenidate prescription world-wide known to the companies, from the International Birth Date (IBD) of the products.

As you also know I have investigated the cases of "suicide attempts or overdoses in some other self-destructive purpose" in connection with ADHD drugs, presented to the Swedish Poisons Information Centre (GIC). This for the population of children and adolescents (10-19) for the years 2011-2015. The investigation revealed that we had *463 individual cases of "suicide attempts or overdoses in some other self-destructive purpose" for these young persons for methylphenidate in these five years!*

In your earlier letter you acknowledged the receipt of this information, and said it was "invaluable in the overall assessment of these events" though providing "limited case by case detail". You also said that these reports were "considered to be spontaneous occurring post-authorisation" and would be "taken into consideration in our ongoing monitoring of the issue of suicidal and self-injurious behaviour with methylphenidate".

It was of course very good to know that the information I had submitted was regarded as "invaluable" and was to be taken into consideration in the coming assessment by MHRA/EMA. But the assessment report from MHRA/EMA raised many serious questions requiring further investigation. We could for example in the assessment report read (page 25): *"Whilst overall the numbers of self-injurious reports may be low, self-injury can have serious consequences."*

Yes, self-injury can *indeed* have serious consequences, *but* what about *"overall the numbers of self-injurious reports may be low"*? I have revealed and presented alarming data about 463 individual cases (10-19) of self-injurious behaviour for methylphenidate in little Sweden (2011-2015) – not exactly a "low number"!

So what do the pharmaceutical companies actually report to the MHRA/EMA; what are the figures about suicides, suicidal behaviour and self-injury *forming the basis for the assessment* by the agencies? How could it be – considering my alarming data from little Sweden – that the instances of self-injury could be deemed to "be low" in the world-wide prescription of these drugs, from their birth?

The secrecy stamp on reported suicides and self-harm

The secrecy stamp first made it impossible to get an answer to any of these questions.

The Swedish Medical Products Agency (MPA) got the Periodic Safety Update Reports (PSURs) from pharmaceutical companies in the beginning of 2017, but refused to release the data about the *number* of suicides, suicidal behaviour and self-injury in these reports. The MPA explained that the MHRA had objected to release the data about the *number* of reported cases of suicidal behaviour and/or self-harm contained in these reports.

It's been said (Goldacre, Bad Pharma, 2012) that drug regulatory agencies have *a "dangerous obsession with secrecy"*, and what could be a better example of this than putting a secrecy stamp on the cumulative number of suicides, suicide attempts and self-injurious behaviour reported by the manufacturers of methylphenidate drugs. Drugs that we know have been involved in 463 cases of "suicide attempts or overdoses in some other self-destructive purpose" for children and adolescents in Sweden.

The MPA even explained that the release of these data – *just the number of cases* – would cause disturbance in Sweden's relations with another country (UK)!

I don't know who at the MHRA decided that this information was sensitive to such a degree that it would hurt the relations between Sweden and the United Kingdom would it be released. What I *do* know is that it would have been impossible to compare the data reported by the pharmaceutical companies with my data from Sweden – had the MHRA and MPA been *successful* in their "dangerous obsession with secrecy".

The newly updated investigation for Sweden

I have now updated my investigation for Sweden up to 2016 and can report:

- 553 children and adolescents (10-19) made suicide attempts with methylphenidate or took overdoses of the drug in some other self-destructive purpose in the years 2011-2016, (data from the he Swedish Poisons Information Centre, GIC).

- Only 3 (!) of these 553 cases were reported to the adverse events register at the MPA.

In your November letter you said the earlier data I gave, though "invaluable", provided "limited case by case detail". In order to give even more valuable data to the MHRA/EMA review I can provide the following data for the added 82 individual cases for 2016:

- 73 of the 82 cases (90%) came from Health Care Personnel (HCPs), and concerned children and adolescents requiring handling in emergency room; these cases should in other words be seen as *serious* adverse events.

- Only one (a 14-year old girl taking Ritalin) of these cases were reported, as required, to the adverse events register at the MPA.

- Concerta was the drug mentioned in 63 of the cases, Ritalin in 14, Medikinet in 8 and Equasym in 3.

- Some examples from the notes for individual cases:
  "hard to breath …heart beating",
  "14 of 18 mg Concerta",
  "feel strange and does not want to live anymore",
  "hope she will die",
  "pain in the heart and cannot breath properly",
  "18 of 54 mg Concerta",
  "hallucinating",
  "not possible get in contact with",
  "11 Concerta 54 mg with suicide purpose",
  "with suicide purpose".

It should be noted that the Swedish Poisons Information Centre (GIC) is an agency administratively *under* the Medical Products Agency (MPA). The MPA can without much effort make a full evaluation of all the 553 cases presented to the GIC for the years 2011-2016.

It should most definitely be noted, as mentioned earlier, that only 3 (!) of the 553 cases (0.5%) were reported to the adverse events register – all of them should have been reported.
In addition to the data above, about suicide attempts and self-injurious behaviour, we should add some words about the *number of completed suicides* in Sweden in connection with methylphenidate treatment. The main purpose with this note is to be able to *compare* the figures with those reported by the pharmaceutical companies.

We find for the year 2015:

- 33 persons in Sweden committed suicide with methylphenidate in their blood at the time of death; 10 of these persons were in the age group 15-24 (data from toxicology analyses done by the National Board of Forensic Medicine).

- *None* of these cases were reported to the adverse events register as a suspected adverse event.

What did the pharmaceutical companies report to the MHRA/EMA?

And we come to *the data reported by the pharmaceutical companies to the MHRA/EMA.*

These are the figures about suicides, suicidal behaviour and self-injury forming the basis for the MHRA/EMA assessment.

The figures so sensitive that it would hurt the relations between Sweden and the United Kingdom would they be released.

The figures about *all* cases of self-injurious behaviour (including suicides and suicide attempts) in connection with methylphenidate prescription world-wide, known to the companies, from the International Birth Date (IBD) of the products.

Completed suicides:

Concerta (Janssen) 43
Ritalin (Novartis) 40
Equasym (Shire) 23

In total: 106

Suicide attempts, self-injurious behaviour*:

Concerta (Janssen) 154-347
Ritalin (Novartis) 93-241
Equasym (Shire) 37-82
Medikinet (Medice) 21-39

In total: 305-709

***** After long negotiations with the European Medicines Agency (EMA) I have finally got access to these figures. However EMA cannot give data about *the number of individual cases* for suicide attempts, suicidal behaviour, intentional self-injury, intentional overdose – only *the total of reported adverse events.* As *one* individual can fall in more than one of these categories I have had to report it as above. The number of reports of self-injurious behaviour (including all categories) is in other words *minimally* 305 and *maximally* 709.

These are the cases of suicides, suicidal behaviour and self-injury forming the basis for the MHRA/EMA assessment.

Let's make it even clearer by presenting these figures about methylphenidate and the ones from Sweden in a table:

Number of cumulative cases of self-harm world-wide reported by the pharmaceutical companies	**Number of cases of self-harm Sweden for children and adolescents (10-19) 2011-2106**
305-709	553
Number of cumulative cases of completed suicides world-wide reported by the pharmaceutical companies	**Number of cases of completed suicides found in toxicological analyses in Sweden for 2015**
106	33

The MHRA/EMA assessment is based on false and completely unreliable data

I have with *limited* resources (the Freedom of Information Act) proved that the MHRA/EMA assessment is based on false and completely unreliable data.

I have also proved that the "dangerous obsession with secrecy" includes the hiding of these data about suicides, suicidal behaviour and self-injury – easily exposed as false if made public.

The MHRA/EMA is looking *in the wrong direction*, and can let the pharmaceutical companies conclude that the number of self-injurious reports is *low*, and so can continue to say that there are no reasons to be concerned.

My concluding questions:

1. Will you make sure that the updated information I have given about Sweden is right away included in the investigation and is given full attention?
2. Will you make sure that the Swedish MPA (with all its resources), for the current assessment procedure, is investigating and reporting the *full* data with *all relevant details* about suicidal behaviour and self-injury reported to the Swedish Poisons Information Centre (GIC) for *all age group*s and *all years*?
3. Will you make sure that true and reliable data from trustworthy authorities (like the Swedish GIC) in the concerned member states are included in the assessment procedure, and that these reliable data are taking precedence over the false and unreliable data submitted by the pharmaceutical companies?

Yours sincerely,

Janne Larsson
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Sweden
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Those not familiar with the Concerta scandal should read the full story, starting with page 19, the letter from 14 February 2014
http://jannel.se/MHRA.Concerta.July2016.pdf

1. EMA/MHRA, "Lead Member State PSUR updated preliminary assessment report Methylphenidate", released in June 2016, http://jannel.se/methylphenidatePSUSA2015.pdf (see page 7).

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Janne Larsson
Sent by email:

14 November 2016

Dear Mr Larsson

Thank you for your emails dated 31 July 2016 and 12 October 2016. Issues relating to the use of methylphenidate, and more specifically Concerta, in adults have been addressed in previous correspondence and I have nothing further to add.

You have noted that there is an overall concern regarding the issue of suicides, suicidality and self-harm in connection with methylphenidate.

To clarify, the independent analysis of suicidality undertaken by Life Science Services on behalf of five Market Authorisation Holders (MAHs) presented in Periodic Safety Update Single Assessment (PSUSA) assessment report dated 09 June 2016, examined those cases reported during clinical trials. The report identified cases of suicidality in the clinical trials in both methylphenidate and placebo-treated patients. This analysis did not take into account spontaneous post-authorisation reports.

The Pharmacovigilance Risk Assessment Committee (PRAC) considered the possibility that those patients involved the clinical trials would have been given greater emotional support than in normal clinical practice and hence the data would not necessarily be reflective of the pattern of reports from patient experience outside a clinical study. The current Summary of Product Characteristics (SmPC) and patient leaflet contains warnings of the risk of suicidal tendency. In a further evaluation, the PSUSA identified spontaneous reports of self-injury that may not be directly associated with suicidality; therefore PRAC agreed that the MAHs undertake a cumulative review of their spontaneous post-authorisation data to be provided in the next PSUR.

Cumulative patient exposure to methylphenidate medicines is extensive, exceeding 25 million patient years of treatment. Therefore individual numbers of cases observed are low in comparison to the overall patient exposure. In spite of this, the final PRAC conclusion remains that the reporting of these behaviours are a safety concern which require further review.

Thank you for the data that you have extracted from the Swedish poisons information centre (GIC) identifying 463 reports of self-destructive action. It should be recognised that the information taken from poison centres, whilst invaluable in the overall assessment of these events, also provide limited case by case detail. Regardless of this, the reports are considered to be spontaneous occurring post-authorisation. These would not routinely have been reported directly to the MAHs therefore the data you provided will be taken into consideration in our ongoing monitoring of the issue of suicidal and self-injurious behaviour with methylphenidate.

Yours sincerely



Dr Ian Hudson,
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