

# Probable neuropsychiatric toxicity of polyethylene glycol: roles of media, internet and the caregivers

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## Summary

**Background and aim:** To investigate the nature, origin and extent of reported neuropsychiatric side effects of polyethylene glycol 3350 (PEG, MiraLax<sup>®</sup>) leading to avoidance of this laxative by parents and caregivers.

**Methods:** We analysed (a) Federal Drug Administration (FDA) Adverse Effect Reporting System (AERS) data. (b) Google Search<sup>®</sup> and Google Trend<sup>®</sup> analysis of internet search trends of PEG side effects and (c) Surveys of US paediatric gastroenterologists. The data was analysed by descriptive statistics, chi squared tests with Benjamini-Hochberg procedure.

**Results:** Between 2007 and 2017, 1564 adverse symptoms (AS) were reported on 645 children between the ages of 0-21. Of these, 919 (58.75%) were neurological, 770 of these were neuropsychiatric (83.8%), such as anxiety, anger, abnormal behaviour, etc. As media reports for AS were released, we found (a) a spike in internet traffic related to PEG AS and (b) a marked increase in AERS reporting; chronologically coinciding with release of media reports on AS. The internet activity has remained above the baseline since then. Of 149 paediatric gastroenterologists surveyed, 25 (16.8%) recalled neuropsychiatric symptoms reported by parents, PEG refusal was reported by 63.3% (76/120), significantly more by those reporting neuropsychiatric symptoms ( $P = 0.03$ ).

**Conclusions:** The PEG refusal reported by paediatric gastroenterologists was temporally related to an unprecedented and sustained spike of internet activity that immediately followed multiple media reports on PEG AS. It appears that negative public perception triggered by media reporting and amplified by internet activity has resulted in increased AERS reporting and parenteral refusal of PEG.

## 1 | INTRODUCTION

A sustained negative perception about Polyethylene glycol 3350 (PEG; MiraLax<sup>®</sup>) among paediatric caregivers has long been known

but never documented. PEG is a well-established treatment of constipation in children.<sup>1,2</sup> Several studies have confirmed its efficacy, safety and superiority over other commonly used laxatives in children.<sup>1,3-6</sup> However, due to a lack of long-term safety data in children

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and reports of minute amounts of toxic metabolites in the blood, the Federal Drug Administration (FDA) had issued a warning on the safety of long-term use of polyethylene glycol (PEG) in children.<sup>7</sup> The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) put out a statement in 2015 clarifying the FDA statement.<sup>8</sup> In February 2017, television segments and social media postings reported anecdotal neuropsychiatric side effects of PEG in children, such as change in behaviour, anger, etc.<sup>9-12</sup> Sporadic reports surfaced that many parents and caregivers were now reluctant to use PEG thereby limiting treatment options for constipation in children. This appeared to be a health care controversy with little information on the existence, extent and scope of the problem and scientific data to support either side. In this study, we tried to look objectively at the available information on the extent and genesis of this controversy. Our goal was to document if aversion to use of PEG was real and if so if it was driven by the internet or scientific data. We analysed the FDA data bank on reported side-effects of PEG; trends, timing and geographical locations of internet activity, as well as the opinions of paediatric gastroenterologists via questionnaire. To the best of our knowledge, no other report examined the existence and dynamics of PEG refusal as it exists in the public domain. Studies sponsored by FDA or National Institute of Health (NIH) do not address this important clinical issue.

## 2 | MATERIALS AND METHODS

For this study we analysed three different sets of data:

We obtained the FDA Adverse Effect Reporting System (AERS) data on PEG 3350 between 2007 and 2017 in subjects between 0 and 21 years of age. For analysis of the data, we divided the symptoms into neurological and non-neurological categories. The neurological side effects were subdivided into purely neurological where there were physical signs and symptoms indicating organic brain disease such as seizure, sensory disturbance, etc, and neuropsychiatric involving psychological or behavioral components such as anxiety, anger, mood swings, etc.

We did a time line analysis of media reporting and internet activity using Google Search<sup>®</sup> and Google Trends<sup>®</sup> tools.

Google Trends data is an unbiased sample of normalised Google search data. It reveals interest in a particular topic as a proportion of all searches on all topics on Google at that time and location. The normalisation allows comparison of different dates, different countries or different cities. The index spikes indicate a sudden acceleration of search interest in a topic, compared to baseline search volume.<sup>13</sup>

We investigated the trend of visited websites that contained the search terms MiraLax<sup>®</sup>, PEG 3350, PEG 4000, laxatives, side effects and children/kids. This timeline was correlated with past media events involving PEG 3350 and that in February 2017. The later was correlated with FDA AERS reporting activity.

Between March and October 2017, we conducted a survey of paediatric gastroenterologists practicing in the US about their personal experience with the side effects of PEG 3350 as well as the parental

attitude toward use of PEG for their children. The Survey Monkey platform was used for data collection (See Questionnaire online). The questions were divided into two parts: the first part inquired about their recollection of seeing neuropsychiatric side effects associated with PEG 3350 administration. The second part requested data prospectively from a work week. In this section more details on the use of PEG and adverse effects were sought. A professional bulletin board, personal emails and phone calls were used to request participation. Those who consented to participate and eligible were issued individualised invitations. The data was downloaded and statistically analysed.

### 2.1 | Statistical analysis

We used descriptive statistics to understand the basic features of the reported adverse effect symptoms by gender and age with Neuro and Non-neuro symptoms. For different Neuro and Non-Neuro symptoms a chi-squared test was done to determine if the variables were related to each other.  $P < 0.05$  was considered as level of significance. Moreover, to control the false discovery rate we performed Benjamini-Hochberg procedure. Adjusting the false discovery rate controls the fact that sometimes small  $P$ -values ( $< 5\%$ ) happens by chance, which can lead to incorrectly significant association between the variables. In other words, we have controlled the false discovery rate (Type I error).

## 3 | RESULTS

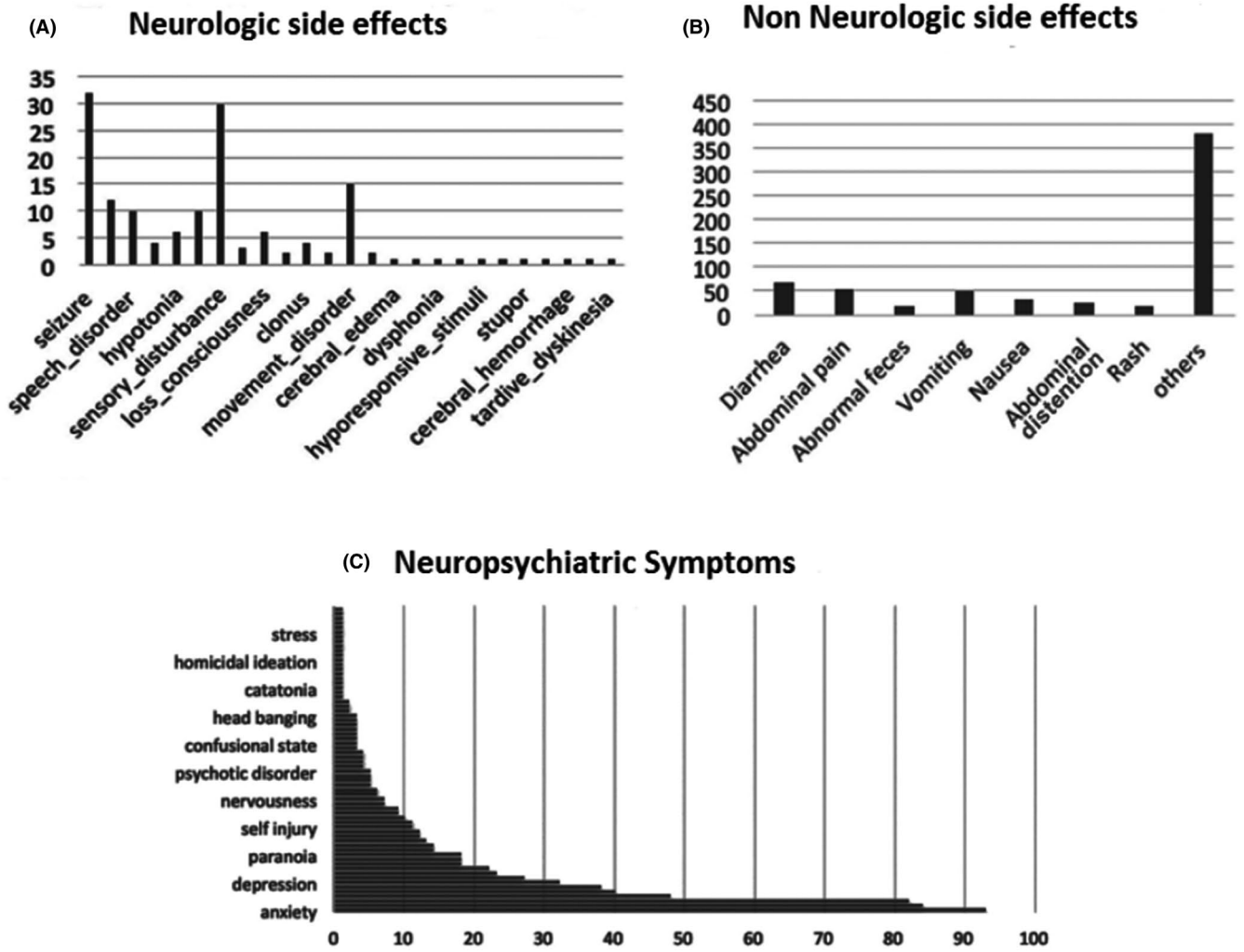
### 3.1 | FDA database analysis

Between 2007 and 2017, 20 536 adverse effect symptoms were reported, of which 1564 involved 645 children. Multiple adverse reactions in the same subject were reported frequently. Three hundred seven children were males, 269 (41.7%) were in the age group of 0-5 years, 204 (31.6%) were between 6 and 10 years, 133 (20.6%) in the 11-17 years' age groups and 39 (6%) were aged between 17 and 21 years. Out of 1564 adverse reactions reported, 919 (58.75%) were neurological, and 770 of these were neuropsychiatric in nature (83.8%). A summary of neurological, non-neurological and neuropsychiatric symptoms is presented in Figure 1A-C respectively. Affective disorder was more common in females ( $P = 0.004$ ) and in the 6 and 10 years' age group ( $P = 0.0003$ ). Males were more likely to be autistic ( $P = 0.0062$ ), especially in those 5 years of age and younger ( $P = 0.0015$ ).

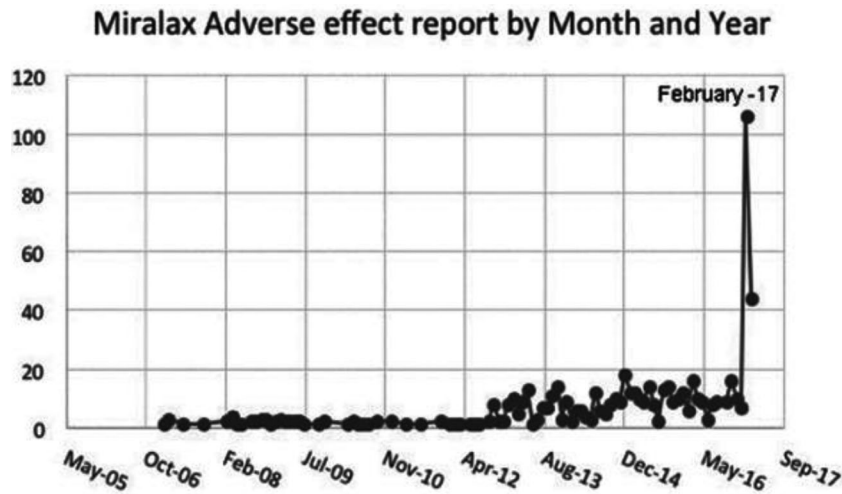
To explore if the timing of media reports and website searches correlated with an increase in the FDA's reported side effects, we plotted adverse effect report by month and year. The trend clearly identified a marked spike in reporting that coincided with the airing/publishing of the press reports (Figure 2).

### 3.2 | Timeline analysis

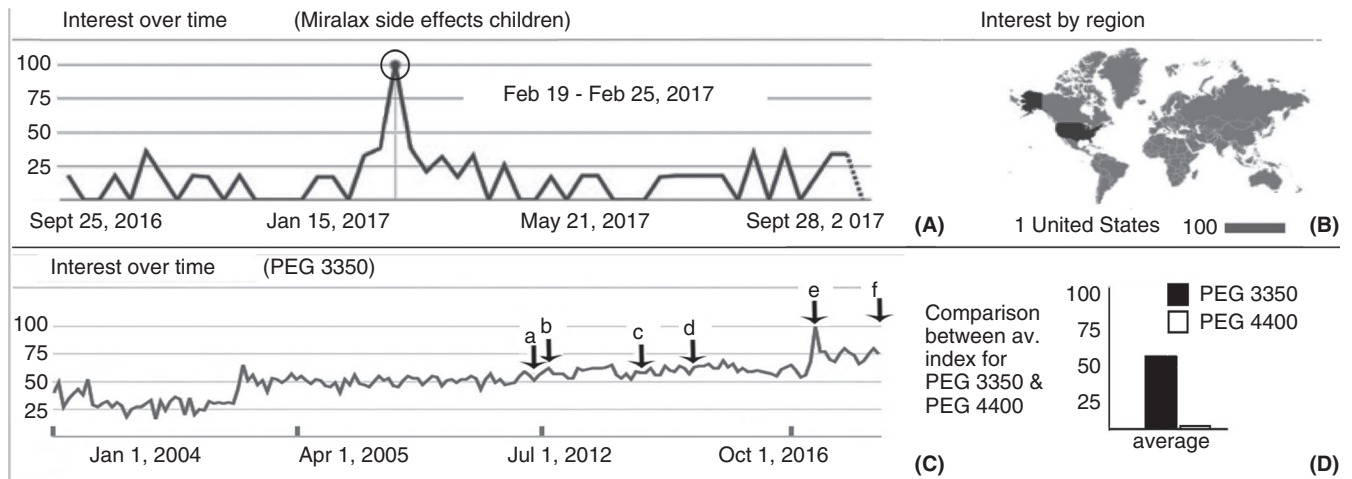
We found a clear spike in the number of visitors to such websites during February 19-25, 2017 (Figure 3A). These dates



**FIGURE 1** Adverse Effects of PEG 3350. A, Neurologic side effects. As reported in the Federal Drug Administration (FDA) Adverse Reporting System (AERS) data. B, Non Neurologic side effects. As reported in the Federal Drug Administration (FDA) Adverse Reporting System (AERS) data. C, Neuropsychiatric side effects. As reported in the Federal Drug Administration (FDA) Adverse Reporting System (AERS) data



**FIGURE 2** Miralax adverse effects by month and year



**FIGURE 3** Internet use trends. Time line Miralax adverse effect (A); Geographical location (B), Interest associated with Major PEG related events (C); Comparison of interest between PEG 3350 and PEG 4000 (D)

exactly coincided with the release of the media reports. The spike in interest in the topic was limited to the United States (Figure 3B)<sup>14</sup> “ Figure 3C shows the historical data on the numbers of visitors associated with important PEG associated events reported in the media. As can be seen in this figure, each ‘event’ produced a spike, but none as high as the reports from February of 2017. Indeed, the average index for PEG 3350 has remained higher to date since those postings were released (Figure 3C), suggesting it has had a lasting impact. It is clear from Figure 3D that the interest in PEG 3350 (used in the USA) was much higher than PEG 4000 (used in Europe); further confirming the geographical boundaries of the surge in internet traffic. Comparing the time line of increased FDA AERS reporting and internet activity showed a strong temporal correlation (Figures 2 and 3A).

### 3.3 | Survey of paediatric gastroenterologists in the USA

There were 149 respondents, 142 MDs and 7 nurse practitioners. 101 were in academic practice while 15 were in group practice, 29 were hospital employed and 4 were in solo practice. 25 (16.8%) reported neuropsychiatric symptoms, mostly as reported by parents. Just three respondents reported large majority (20 of the 30) of the children with neuropsychiatric symptoms. The majority of the patients had neuropsychiatric symptoms such as behavioral changes and attention deficit disorder. Caregivers requested not to start or to discontinue PEG to 76/120 (63.3%) respondents. Practitioners who saw more children on PEG reported more neuropsychiatric symptoms ( $P = 0.02$ ). Those who reported neuropsychiatric symptoms were more likely to be requested not to start or discontinue PEG ( $P = 0.03$ ). Fifteen practitioners (12.5%) reported more than 10 patients each with such requests. Practitioners who saw more patients on PEG tended to have more requests for not starting/discontinuing PEG ( $P = 0.0125$ ).

## 4 | DISCUSSION

The explosion of information available in the public domain through the internet has revolutionised life in many ways. That includes invasion of the previously insular world of academic medical research and, by extension, medical care by laypersons. Patients and parents of children feel empowered by the internet to be actively involved in medical decision making.<sup>15</sup> While this has been generally welcomed, accepted and incorporated into medical practice protocols by clinicians, concerns have been raised on the quality of the information that mould public perception. In the academic medical model; the available literature is scrutinised by trained specialists on the quality of data based on research design and execution within strict parameters and given appropriate weightage in decision making.<sup>16</sup> However, on the internet, one personal experience or opinion can ‘go viral’ with multiple ‘copycat’ postings online or in social-media; anecdotal experience thereby may drive the decision making process without critical review or proof. One of the examples of this dynamics is the current controversy about the use of PEG in children.

Though PEG is being extensively used in children, there had always been concerns as it is the polymerised product of a toxic chemical.<sup>17</sup> FDA statements and media reports further validated the already suspicious caregivers’ belief about ‘hidden’ side effects of PEG. Available literature does not support such a claim though no study has specifically addressed neuropsychiatric side effects. There is sparse literature on side effects on PEG 3350. The reported side effects from these reports included: electrolyte abnormalities, abdominal pain, diarrhoea, nausea/vomiting, bloating/flatulence, and irritation of the anal area, bloating and gases or abdominal pain, allergy, raised ALT and one case with thirst, fatigue and nausea.<sup>4,18-21</sup> One recent large study on clinical use of PEG reported one patient with headache as the only neurologic adverse effect while another fairly large randomised trial failed to document significant adverse reactions on long-term maintenance therapy.<sup>22,23</sup> A recent study has documented PEG metabolites in children on PEG and in those who

were not. These PEG related chemicals were not associated with any significant side effects, especially neuropsychiatric ones.<sup>24</sup>

In our study, we collected and analysed available objective data to understand the origin and possible scientific validity of information leading to this phenomenon. We documented, for the first time, that PEG aversion is real; about two third of paediatric gastroenterologists polled reported not using or discontinuing PEG at a caregiver's request for potential side effects. As to the cause of this phenomenon, our study provides an interesting overview. The internet data showed a significant spike of activity that coincided chronologically and geographically (within the US) with the anecdotal media reports. We also noted increased reporting of adverse reactions at FDA AERS system during these spikes. This may denote increased awareness and/or consumer activism. Many patients were reported to have multiple adverse reactions, mostly neuropsychiatric, concurrently. The reported adverse reactions could not be correlated or verified due to the very nature of the database. More prevalent neuropsychiatric side effects such as behavioral changes and apathy are subjective and difficult to prove without a careful psychological evaluation especially in young children.

Furthermore, the possibility of over reporting to AERS by caregivers made sensitive to 'toxic' effect of PEG by the media and internet activities cannot be ruled out. It is also not clear if those symptoms were pre-existing or arose de novo due to PEG use. Constipation itself or its treatment with PEG can cause symptoms such as abdominal pain, gas, bloating and other forms of abdominal discomfort. Change in behaviour due to these symptoms, especially in young non-verbal children, might have been perceived by parents as neuropsychiatric manifestations.<sup>25</sup>

The data from our survey of paediatric gastroenterologists reveal that about 16% of respondents encountered subjective reporting of neurological side effects in their practices, but about 2/3rd faced PEG aversion. So it seems that PEG aversion was driven by something other than adverse reaction occurring while being treated by the care giver; media and the internet being the most likely possibilities.

However, our data sources have significant limitations. The FDA AERS system reports suffer from sampling bias, lack of verification, inability to seek clarifications and follow-up data. Internet activity data is only a gross indicator website use. Our survey of paediatric gastroenterologists might have had sampling bias; participation was voluntary and those with a special interest in this issue might have been motivated to participate. Most of the adverse reactions were reported by the parents rather than being seen or verified by the clinician. It was not possible to verify symptoms and seek clarifications. Our data also suggest that there might have been some personal biases as only three respondents reported two third of the patients with neuropsychiatric side effects. Lastly, as members of the medical profession, the authors may have some inherent bias against the interference of caregivers in the medical decision making process.

We conclude that the recent PEG 3350 aversion was real. It was fuelled, at least in part, by media coverage of anecdotal experience

and subsequent amplification by internet and social-media posts. It is not even clear that the large number of neuropsychiatric side effects reported to the AERS system were pre-existing or caused by the therapy or exacerbated by it. Regardless of their scientific merits, these public perceptions are pivotal in continuing use of this useful laxative. Though the current scientific literature does not support the public perception, longitudinal studies have not been done to address these specific symptoms, hence allowing the controversy to live on. The only way to address this issue is to organise a national prospective multicentre study, addressing some of the questions raised in this preliminary survey of available data.

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## AUTHORSHIP

*Guarantor of the article:* Dr Sudipta Misra MD.

*Author contributions:* Dr Hussain has collected data, helped writing the first draft and reviewed the final draft. Dr Belkind-Gerson has helped in conceptualising the study, collected and analysed data, helped write the first draft and reviewed the final one. Dr Chogle has collected and analysed data and reviewed and modified the final draft. Dr Bhuiyan analysed the data and helped write first draft and reviewed and modified the final draft. Dr Hicks has collected and helped analyse the data. He has reviewed the final draft. Dr Misra has conceptualised the study, collected data, helped analysing them, wrote, reviewed and modified the final draft. All the authors have reviewed and approved the final manuscript.

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