Clinical and Practical **Psychopharmacology**

Methylphenidate and the Risk of New-Onset Seizures

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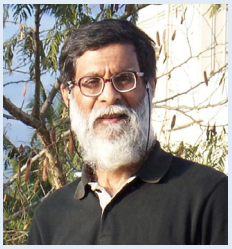

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is usually treated with stimulant drugs such as methylphenidate (MPH). ADHD is associated with an increased risk of seizures and, in this context, concerns have been expressed that stimulant drugs, including MPH, may increase the seizure risk. However, 4 large observational studies have found that ADHD drugs in general and stimulant drugs in particular are not associated with increased seizure risk and may, in fact, be associated with a reduced risk of seizures; these studies were largely conducted in children and adolescents, including those with epilepsy, with or without other brain comorbidities. The findings were obtained in both between-subjects and within-subjects analyses; the latter controlled for time-invariant inadequately measured, unmeasured, and unknown confounds. These reassuring results support the results of many small, short-duration trials that found that MPH was not associated with increased seizure risk. One other observational study however found that MPH was indeed associated with an increased risk of seizures, but only during the first 30 days after drug initiation; there was no increase in risk in earlier or later time windows. There are many reasons why this single finding should be viewed with reservation; in any case, even if the finding is valid, the absolute risk of seizures with MPH appears to be very low. It is therefore reasonable to conclude that MPH may be safely used in children and adolescents, even those with a current or past history of epilepsy; however, prudence dictates that attention be paid to potential seizure triggers during the first month of treatment. This risk needs to be specifically reexamined in future research.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is not uncommon in children and even adults. In children, for example, a meta-analysis of 10 epidemiologic studies from 8 countries found that the prevalence of ADHD in 18,282 children aged 1–7 years was 2.7% (95% confidence interval [CI], 1.3%–5.8%); when data from 2 outlying studies were excluded, the prevalence was 4.3% (95% CI, 2.5%–7.2%).[1] In adults, a study of health care data in Northern California found that 1.1% of 5,282,877 adults had a diagnosis of ADHD.[2]

Psychostimulants are the most effective treatments for ADHD, and methylphenidate (MPH) may be the best among these for children and adolescents when safety and efficacy are both taken into account.[3] MPH treatment of ADHD is associated with many adverse effects.[4] Are seizures included among these adverse effects? This is an important question because ADHD is itself associated with seizure disorder.[5,6] This is also a difficult question to answer because most studies of MPH listed a past history of seizures as an exclusion criterion for recruitment[4]; MPH would therefore have been prescribed to patients with a lower baseline seizure risk, resulting in a distortion of the association, if any, between the drug and the risk of seizures.

Several small and large studies, including population-based observational studies, have now examined whether ADHD treatments in general and MPH in particular are associated with an increased seizure risk in persons, especially youth, with and without ADHD and in those with and without a past or current history of seizures. These studies are briefly examined.

ADHD Medications and Seizure Risk

In a study of children and adolescents, aged 6–17 years, enrolled in a US health plan, 13,398 subjects who initiated treatment with atomoxetine were propensity score–matched with 13,322 subjects who initiated treatment with stimulant medications. The 6-month seizure risk (97 events) in atomoxetine-treated subjects did not differ significantly from that in stimulant-treated subjects (relative risk [RR], 0.72; 95% CI, 0.37–1.38). The risk was nonsignificant based on initial cohort assignment, as well (RR, 0.90; 95% CI, 0.54–1.49).[7]

In a retrospective cohort study based on billing records from 26 US states, Liu et al[8] identified 18,166 users and 54,197 nonusers of psychostimulant drugs among children (age, 18 years and below) with epilepsy. Among the users, 63.3% had used MPH. After adjustment for confounders, neither current use (hazard ratio [HR], 0.95; 95% CI, 0.83–1.09) nor former use (HR, 0.99; 95% CI, 0.85–1.15) of psychostimulants was associated with the 12-month risk of seizure-related hospitalizations. Importantly, in additional analyses, the HRs were not significantly higher also in children with cerebral palsy, congenital nervous system anomalies, or intellectual disability relative to those without these conditions.

In a US study based on drug claims,[9] data were extracted for 801,831 patients with ADHD. The median age of the sample was 17 years. In a within-subjects design, the risk of seizures was lower during periods of

ADHD medication use than during periods of nonuse for both persons with (n = 9,739; odds ratio [OR], 0.71; 95% CI, 0.60–0.85) and without (n = 792,099; OR, 0.51; 95% CI, 0.43–0.62) a past history of seizures. The odds were significantly lower in men as well as in women, in most age bands, specifically with stimulant medications, and in many but not all other sensitivity analyses. In no analysis were the odds of seizures significantly raised. In analyses of cumulative exposure to ADHD medication during the previous 2 years, there was no increase in the concurrent or long-term odds of seizures in persons either with or without a past history of seizures; in fact, the odds were significantly decreased in some analyses. This was true for the associated sensitivity analyses, as well.

In a Swedish, population-based register study,[10] 6,773 youth, aged 18 years and below, were identified, all of whom had epilepsy. There were 995 individuals who initiated ADHD medication. In within-subjects analyses, relative to the same period in the previous year, the seizure risk was not elevated in the first 12 weeks (incidence rate ratio [IRR], 0.95; 95% CI, 0.60–1.56) or in the next 12 weeks (IRR, 1.05; 95% CI, 0.65–1.68) after ADHD medication initiation. In the same study, in analyses of 11,754 seizure events in 21,557 individuals, in neither population-level analyses nor within-individual (on vs off medication periods) analyses was ADHD medication use associated with increased seizure risk. This finding was true in the full cohort, in the full cohort after adjusting for concurrent anticonvulsant medication use, in individuals with and without concurrent anticonvulsant medications, in males and in females, and in individuals with ADHD with or without additional neurodevelopmental disorders. In fact, in several of these secondary analyses, use of ADHD medication was associated with significantly reduced seizure risk. However, separate data for MPH were not presented, and the proportion of MPH users in the different analyses was not clear.

Methylphenidate and Seizure Risk

MPH lowers the pentylenetetrazol seizure threshold in rats.[11] MPH may increase abnormalities in the electroencephalogram in youth with ADHD and epilepsy.[12] However, a review[13] of 7 prospective studies (pooled N = 263) conducted on patients with comorbid epilepsy and ADHD concluded that MPH was effective in treating ADHD symptoms and that MPH did not increase the seizure rate. A limitation of these conclusions was that all the reviewed studies had shortcomings that included small sample size and low baseline seizure rates. Five of the studies were 8 weeks or less in duration. No study included a parallel arm control group.[13] A more recent trial[14] also found that MPH did not increase the seizure rate; however, this study was also small (n = 28) and short (1 month). Other small studies with similar findings have also been published.

Only 1 study[15] has specifically examined the seizure risk during the first month as well as in earlier and later time windows relative to MPH initiation in seizure-free youth; this study is unusual in that it is also the only study to have found a significantly increased seizure risk associated with MPH initiation. This study is therefore examined in some detail in the next section.

Methylphenidate and Seizure Risk in Different Time Windows

Man et al[15] described a self-controlled case series study using data extracted from an electronic health record database in Hong Kong. There were 29,604 subjects who had received MPH during the study period (2001–2017). Cases (n = 269) comprised youth aged 6–25 years who had previously been seizure free, who had received at least 1 prescription for MPH during the study period, and who had experienced at least 1 (their first) non-febrile seizure during the study period.

The median (interquartile range [IQR]) age of the sample was 6 (6–6) years at baseline. The sample was 74% male. Slightly more than half (58%) of the sample had a diagnosis of ADHD. The median (IQR) daily dose of MPH was 20 (15–30) mg. Subjects were followed for a mean of 10.7 years, during which time they were exposed to MPH for a mean of 2.2 years.

There were 69 seizure events during 589 patient-years of exposure to MPH and 200 seizure events during 2,286 patient-years of MPH-free follow up. In the entire sample of 29,604 subjects exposed to MPH, the risk of seizure was 4.4 per 10,000 patient-years.

Relative to periods of no exposure to MPH, the risk of seizures was significantly increased in the first 30 days after MPH initiation (IRR, 4.01; 95% CI, 2.09–7.68) but not in the 90 days before treatment initiation (IRR, 1.60; 95% CI, 0.88–2.92), or during days 31–180 of treatment (IRR, 1.13; 95% CI, 0.56–2.25), or during subsequent treatment (IRR, 1.38; 95% CI, 0.92–2.07).

In additional analyses, neither use of antidepressant nor use of antipsychotic drugs was significantly associated with seizure risk, even when examined in combination with MPH. Other subgroup and sensitivity analyses presented in the paper and in the appendices mostly supported the primary analyses. However, most of these were underpowered because they were based on too few (or no) seizure events.

Finally, the authors[15] examined whether the risk of skin infections, as a negative control, was associated with MPH exposure. They found that in no time window was exposure to MPH associated with an increased risk of skin infection; use of antidepressant or antipsychotic drugs was also not associated with risk of skin infection.

Critical Appraisal

One strength of the study by Man et al[15] is that patients served as their own controls; therefore, the effects of inadequately measured, unmeasured, and unknown time-invariant confounding variables would cancel out when MPH-exposed and MPH-unexposed periods were compared (time-invariant confounding variables are confounding variables in individual subjects that were present at all times

in those subjects, regardless of MPH exposure). Another strength of the study is that the authors adjusted the analyses for time-varying confounds, such as age, season, and use of other psychotropic medications. A further advantage is that subjects were followed up for a sufficiently long period (nearly 11 years, on average) for the event of interest to happen, if at all the risk existed.

The most important limitation of the study is that there was no correction for multiple testing in the many analyses presented, such as the testing of risk in 4 different time windows of MPH exposure. It is therefore possible that the significant increase in risk during the initial 30 days was a type 1 (false positive) error. There are many additional reasons why this finding may have been spurious. One is that if MPH increases the seizure risk through a biological effect, assuming that tolerance does not develop to this biological effect, the effect should be uniform across time, and not present only during the first month of treatment. Next, the dose of MPH was significantly lower (by half) in the initial month than subsequently; it is not logical that lower doses rather than higher doses trigger seizures. Then, MPH has a short half-life, and so every day could be an initiation of MPH after drug washout from the body; this is especially true when weekend or other drug holiday strategies are applied.

There is also the real possibility that, even though subjects acted as their own controls, thereby controlling for time-invariant inadequately measured, unmeasured, and unknown confounds, the analyses could have been biased by unmeasured and unknown time-varying confounds. That is, periods of MPH exposure, relative to nonexposure, might have been systematically associated with environmental and behavioral variables that lower seizure threshold. As an example, MPH may have been prescribed during the school term and stopped during between-term holidays, students may have slept less per day during the school term and more per day during the holidays, and reduced sleep may have been associated with a decrease in the seizure threshold, resulting in seizures in vulnerable persons.[16] It is also possible that MPH was started when risky behaviors emerged and discontinued when risky behaviors subsided (confounding by indication) and that certain of these risky behaviors were seizure triggers. The authors considered that such confounding is unlikely because they estimated that the confound would need to be associated with the treatment and the outcome, each, by a risk ratio of 3.6, after the existing adjustment for confounds. However, such time-varying confounding may yet be reasonably possible if there was more than one unmeasured confound with additive effects.

The study[15] had other limitations, too. For example, most of the analyses were based on a very small number of seizure events and a very small number of patient-years of exposure. The only significant finding, that of increased risk in the first 30 days of treatment, was based on just 10 events in just 20.7 patient-years of exposure. Finally, given that ADHD is itself associated with seizure risk,[5,6] and given that the authors performed a very large number of subgroup and sensitivity analyses, it is puzzling that they did not also examine risks in subjects with and without ADHD.

Readers are asked to note that none of these limitations make the study a poor study; however, the limitations do place restrictions on the extent to which the findings can translate into recommendations for clinical practice.

Interpretation

Previous large observational studies found that ADHD medications in general[9,10] and psychostimulant drugs in particular[7–9] either did not increase the seizure risk[7,8] or actually reduced the seizure risk in main and/or secondary analyses.[9,10] These findings were obtained in children and adolescents,[7,8,10] including children and adolescents with epilepsy or at least a past history of seizures[8–10] and including high risk children and adolescents with epilepsy, such as those with cerebral palsy, congenital nervous system anomalies, or intellectual disability.[8] The findings were obtained from between-subjects[7,8] and within-subjects[9,10] analyses; the latter controlled for time-invariant confounds. Many small studies of MPH in particular, conducted in patients with comorbid ADHD and epilepsy, found that MPH did not increase the seizure risk.[13,14]

Given this background, the possible signal of increased seizure risk in the first month after MPH initiation[15] may be an outlying finding. As discussed in the previous section, there are many reasons why this signal may need to be viewed with reservations; however, the finding should not be dismissed outright because it was obtained in the only study to examine the MPH-specific seizure risk in a within-subjects design and across a long time span. This signal will require examination in future research.

In the worst case scenario, if MPH does increase the seizure risk, the risk is probably very small. In the Man et al[15] study, the risk was 4.4 per 10,000 patient-years; this is like saying that 2,272 patients will need to receive MPH for a year for 1 patient to experience a seizure event. Note that this number is not corrected for the baseline risk of seizures associated with untreated ADHD, and so the risk associated with MPH could be even smaller. Of note, Man et al[15] did not provide information about the absolute risk of seizures specifically in ADHD subjects and specifically in the first month of treatment in the entire sample exposed to MPH.

Points for Consideration

Two large observational studies that employed a within-subjects design found that ADHD medications were associated with protection against the risk of seizures.[9,10] MPH and other ADHD medications are not anticonvulsant drugs, so what might be the reason for this finding? One possible explanation is that ADHD treatments reduce symptoms or behaviors that might be associated with seizure risk. As an example, in a cross-sectional, observational study of children and adolescents with epilepsy and ADHD, MPH was associated with better sleep parameters on parental report as well as actigraphy.[17] Although the supporting

evidence is poor in quality, it is generally believed that insufficient sleep increases the risk of seizures,[16] so better control of ADHD symptoms through improvement in sleep patterns could result in reduced seizure risk.

Take-Home Message

Medications for the treatment of ADHD either have no association with seizure risk or reduce the risk of seizures in children and adolescents, even those with epilepsy. Whereas this appears true for MPH, as well, one recent study suggested that periods of initiation of MPH may be associated with a raised seizure risk during the first 30 days of treatment. There are many reasons to believe that this finding does not represent a cause-effect relationship; however, even if it does, the absolute risk of seizures during MPH therapy is very low, perhaps as low as 1 in 2,272 patient-years of treatment. This, therefore, does not suggest the need for a change in clinical practice; however, prudence dictates that clinicians who initiate MPH should pay special attention to potential seizure triggers during the initial month of MPH therapy.

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