Database Studies and the Pitfall of Imputing Complex Clinical Causality

To the Editor: I read with interest the article by Wang et al[1] on the impact of drug adherence on oppositional defiant disorder (ODD) and conduct disorder (CD) among Taiwanese children diagnosed with attention-deficit/hyperactivity disorder (ADHD). In it, the authors state that "good drug adherence consistently exerted protective effects on ODD or CD." If this is true, it is an extremely important finding, and one that should lead treating physicians to urge parents to ensure their children's ADHD medication compliance by all possible means.

In this database study, the authors found that of 33,835 children diagnosed with ADHD, the one-third of the cohort defined as having good compliance over 90 days of treatment with either methylphenidate or atomoxetine had a lower risk of being diagnosed with ODD or CD over the subsequent 2 years.

The authors' inference of a protective effect of medication on the development of ODD or CD is flawed for 2 main reasons. First, the authors are aware that the diagnosis rates of both ODD and CD imply substantial underdiagnosis. Even after adding those already diagnosed or diagnosed during the 90-day treatment period to the 4.1% and 4.0% diagnosed with ODD and CD, respectively, over the 2-year follow-up period, the resultant rates of 8.85% and 7.29% are still well below those rates established by interview among Taiwanese children with ADHD, cited as 69% and 33%, respectively.[1] The authors acknowledge that it is unclear what selection biases might have affected the rate of ODD and CD diagnoses being documented in their cohort and have listed several possibilities, including frequency of outpatient visits, socioeconomic status, and family dysfunction. Any of these might also have an association with medication compliance.

The second and even more important flaw is that the assertion of a protective effect of medication for subsequent development of both ODD and CD is actually contradicted by the finding that a longer delay in starting medication after a diagnosis of ADHD was also protective. Logically, if consistent medication (good compliance) is protective for ODD and CD, lack of medication (delayed treatment) cannot also be protective.

A far more likely explanation of the correlation between poor compliance with prescribed medication and ODD and CD is that these conditions both predispose to poor compliance. In other words, causality goes in the direction opposite to that suggested by the authors.

A final warning about the pitfall of database studies: even though the study numbers may be appealingly large, extreme caution should be used in imputing complex clinical causality to limited database data of unknown accuracy.

Reference

1. Wang LJ, Lee SY, Chou MC, et al. Impact of drug adherence on oppositional defiant disorder and conduct disorder among patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2018;79(5):17m11784.

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Dr Wang and Colleagues Reply

To the Editor: In our recent study,[1] we suggested that drug adherence in attention-deficit/hyperactivity disorder (ADHD) patients may be beneficial in the prevention of oppositional defiant disorder (ODD) or conduct disorder (CD). We are grateful for the opportunity to respond to Dr Poulton's comments about our study.

First, substantial underdiagnosis of ODD and CD in this study population might be due to selection biases and affect our results. The rates of comorbid ODD and CD in ADHD were only 4.1% and 4.0%, respectively, in our study population, which are indeed lower than those reported in previous studies.[2,3] The low comorbidity rate in our study may be attributed to the case-recruitment criteria. As such, we excluded patients who had an ODD or CD diagnosis prior to their ADHD diagnosis and whose ODD or CD diagnosis was made within 90 days after medical treatment. In addition, the low comorbidity rate might potentially be related to the lack of a systematic assessment in real-world clinical practice, in contrast to epidemiologic studies that use a structured interview to obtain a comprehensive screen of comorbidity and diagnosis confirmation. However, our sensitivity tests indicated that demographic characteristics may not influence the effect of drug compliance on comorbidity rates; therefore, we believe that drug adherence is an independent factor associated with decreased ODD/CD comorbidity rates.

Second, Dr Poulton questioned whether "a protective effect of medication for subsequent development of both ODD and CD is actually contradicted by the finding that a longer delay in starting medication after a diagnosis of ADHD was also protective." Our data showed that diagnosis of ADHD at an older age was associated with a lower risk of developing ODD or CD. A possible explanation for this phenomenon is that age of diagnosis/prescription was also associated with patients' characteristics. For example, patients with greater symptom severity or greater tendency toward disruptive behaviors may seek medical assistance or receive pharmacotherapy earlier than their counterparts with less severity, and this may lead to a lower risk of ODD/CD diagnosis in older patients. Actually, we only reported the results of our sensitivity analyses for drug adherence on the risk of developing ODD or CD, which showed that drug adherence (medication possession ratio $\geq 50\%$ vs $< 50\%$) consistently exerted protective effects on ODD or CD in each stratification (see Table 3 of article). The interval between ADHD diagnosis and medication (comparing < 3 months, 3–12 months, and > 12 months) did not significantly affect ODD/CD risk (see Table 2 of article). Therefore, our results should not be interpreted as showing that "delay in starting medication after a diagnosis of ADHD was also protective."

Finally, we agree with Dr Poulton's opinion: "A final warning about the pitfall of database studies: even though the study numbers may be appealingly large, extreme caution should be used in imputing complex clinical causality to limited database data of unknown accuracy." Indeed, even though we used a large-scale nationwide database to conduct this study, we demonstrated only an association, not necessarily causality, between drug compliance and diagnosis of ODD/CD among youths with ADHD. Randomized controlled design is the gold standard for examining causal inference between these 2 events. However, due to ethical and practical concerns, it is impossible to carry out a longitudinal randomized controlled trial with 2 arms of volunteers (one for good drug compliance and the other for poor drug compliance) to determine the impact of drug adherence on ODD/CD among patients with ADHD. Use of nationwide naturalistic data is the best alternative way to investigate this research topic. We agree that cautious and conservative explanation regarding the causal relationships between persistence of medication treatment and onset of ODD/CD is warranted.

References

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