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The Incidence of Seizures With Antipsychotics

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It is very difficult to get information on uncommon side effects from clinical trials. Various electronic datasets, such as prescription or billing databases, offer opportunities to get some data. Wu and collaborators¹ mined the National Health Insurance program in Taiwan in a sophisticated and methodologically sound analysis to measure the incidence of seizures associated with the use of antipsychotics. They eliminated seizures caused by known diseases, and while that cannot be accomplished perfectly, it offers assurance that the data were not massively driven by the underlying medical disease.

The incidence of seizures is about 0.01 per person-year, so this event is uncommon but not rare. There was a trend ($P = .06$) for second-generation antipsychotics to be associated with a lower risk of seizures. Even with data on almost 300,000 patients or 60,000 person-years, some drugs caused only a few seizures, rendering estimates for many individual drugs unreliable.

After the discovery of chlorpromazine, the pharmaceutical industry developed drugs that were more potent in animal models or at blocking dopamine receptors. Most of the drugs that had a slightly higher seizure incidence in the present study, such as chlorprothixene, thioridazine, clozapine, zotepine, and chlorpromazine, were used in high-milligram doses (and were older drugs). This list roughly corresponds to the observational studies done in the 1950s and 1960s, when the older drugs were studied.² The exception was haloperidol, though the authors suggest this finding may have resulted from a difference in haloperidol metabolism in the Han Chinese versus westerners, as this observation was not found in the WHO pharmacovigilance database. The lowest incidence of seizures was seen with aripiprazole and was based on just 7 cases. The limiting factor on statistical reliability of individual drugs was the number of seizure cases.

Causation should not be inferred from observational data sets. A variety of known epidemiologic biases as well as unknown biases can limit the accuracy of inferences from observational data. The event may be due in a variable degree to predisposing factors of the individual receiving the drug, and that in part determines who may be prescribed the drug. In the study by Wu et al, disorders associated with seizures (mental retardation, autism, alcohol or substance abuse), the presence of chronic renal failure, and the administration of anticonvulsants were associated with a higher incidence of seizures. Individuals with schizophrenia also showed a higher incidence of seizures, possibly due to the larger doses of antipsychotics required.

Another area of bias is cognitive bias. Cognitive biases have been carefully studied by psychologists and behavioral economists, and their existence is documented in a number of controlled studies.³ Indeed, the Nobel Prize in economics was awarded to the psychologist Daniel Kahneman because of the importance of this research to economics. Humans have difficulty evaluating uncommon and rare events. They dismiss such occurrences by assuming they will not occur, or, if such events do occur (and particularly if the event is dramatic), then humans expect such events to occur more commonly than is warranted by the data. Humans can dismiss a rare event, assuming it so rare that it will virtually never happen, but some events can be important, albeit uncommon. Pharmacovigilance then calls attention to events that are considered vanishingly rare but are simply uncommon. In Wu and colleagues' analysis, there were no surprises, but that is worth knowing. Having an approximate estimate of occurrence and knowing the modest differences between drugs provide perspective and help prevent dismissing the possibility of seizure or overemphasizing it.

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