An Assessment for the Risk of Herb-drug Interactions in Adverse Event Reports (AERs) Related to Natural Health Products and Medications Used for Attention Deficit Hyperactivity Disorder

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Concurrent use of Natural Health Products (NHPs) is common in patients using medication for Attention Deficit Hyperactivity Disorder (ADHD). NHPs are generally recognized as safe, however some can lead to adverse events, either alone or when taken concurrently with drugs. Adverse event reports (AERs) submitted to regulatory agencies can be used to evaluate safety of NHPs. Our goal is to identify AERs relating to potential herb-drug interactions and assess them for quality and causality, and to use complementary in-vitro assays to evaluate bioactivity. We systemically searched the FDable database for AERs involving commonly used NHPs with ADHD drugs (stimulants and non-stimulants). We obtained 53 reports from U.S. Food and Drug Administration through the Freedom of Information Act and evaluated their quality using multiple validated scales. We identified 8 AERs using less than 3 substances for causality assessments (4 St. John's Wort, 2 ginkgo biloba, 2 evening primrose oil) completed by four experts using 3 tools. Consensus of causality assessments ranged from doubtful to possible risk of an interaction, with an agreement on lack of information present in the AERs. In-vitro inhibition assays were performed with recombinant enzymes (florescence based) and human liver microsomes (using high-performance liquid chromatography) to determine effects of select NHPs on enzymes involved in ADHD drug metabolism. Preliminary data reveal St. John's wort and ginkgo biloba inhibit recombinant carboxylesterase 1 and that St. John's wort reduces human liver microsome-mediated metabolism of methylphenidate. Overall, causality assessments from high quality reports in conjunction with in-vitro data can aid in evidence-based decision making and fill imperative gaps in the safety of NHPs.