Unwanted Interactions Among Psychotropic Drugs and Other Treatments for Autism Spectrum Disorders

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Autism spectrum disorders (ASD) are pervasive neurodevelopmental disorders affecting approximately 1% of children and characterized by varying degrees of deficiencies in social interactions, concentration, language, learning, and as stereotypic behaviors.[1–3] Many children develop ASD by regression at approximately age 3 years, often after a specific event such as vaccination or infection, although they were developing normally.[4,5] Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures.[6]

Behavioral interventions alone are not sufficient to adequately address the disruptive nature of ASD symptoms and their persistence throughout life.[7,8] Instead, psychotropic drug therapy is typically used to treat irritability, hyperactivity, inattention, obsessive-compulsive symptoms, aggression, and self-injury.[9–11] Many children with ASD also develop seizures with no apparent underlying pathological cause,[12–14] but traditional antiseizure medications seem to worsen ASD symptoms.[15]

Overall, 70% of children with ASD take at least 10 different drugs, dietary supplements, vitamins, or other treatments[10,16–18] including intravenous immunoglobulin.[19] Secretin is also commonly used although it has no effect[20] and could lead to the risk of possible inflammatory complications.[21] There is little attention to unwanted drug-drug or drug-supplement interactions.

ANTIPSYCHOTICS

A cross-sectional study of a child and adolescent psychiatric sample nationwide in Denmark found that the prevalence of treatment with antipsychotic medications was 6.4%.[22] Some pediatric patients were prescribed additional medications, with 24% receiving antidepressants, 8% receiving sedative medications, and 4% receiving psychostimulants.[22] Many children with ASD also take antipsychotic medications.[23] In a national sample of children and adolescents with ASD, the percentage of outpatients being treated with antipsychotic medications was almost 30%.[24]

Risperidone is the only antipsychotic drug with Food and Drug Administration approval for treating aggressiveness and stereotypic and self-injurious behaviors in ASD.[25] This class of drugs also includes haloperidol and the newer "atypical" compounds.[26,27] Aripiprazole is an atypical antipsychotic approved for treating irritability in children with ASD.[28] A review of 21 randomized placebo-controlled trials using psychopharmacologic agents[29] showed that only risperidone for aggressive behavior[30,31] and methylphenidate for hyperactivity[32] produced significant improvement in more than one study.[29] A recent systemic review of medical treatments for children with ASD concluded that only risperidone and aripiprazole had some benefit, but they had significant adverse effects.[33] For instance, they result in significant weight gain, whereas haloperidol use is limited owing to higher risks of extrapyramidal effects and tardive dyskinesia. Another study of children with ASD from a national registry showed that 35% of children with ASD received psychotropic medications, but adding a second-generation antipsychotic to the stimulant did not have any significant additional benefit on any of the parameters studied.[34] Moreover, the long-term safety of antipsychotics in children remains unknown.[23]

ANTIDEPRESSANTS

Many children with ASD are also prescribed antidepressants, especially selective serotonin reuptake inhibitors (SSRIs).[9] However, 2 recent reviews concluded that there is insufficient evidence for any benefit of SSRIs or other psychotropic drugs in ASD.[33,35] In fact, the results of a recent trial
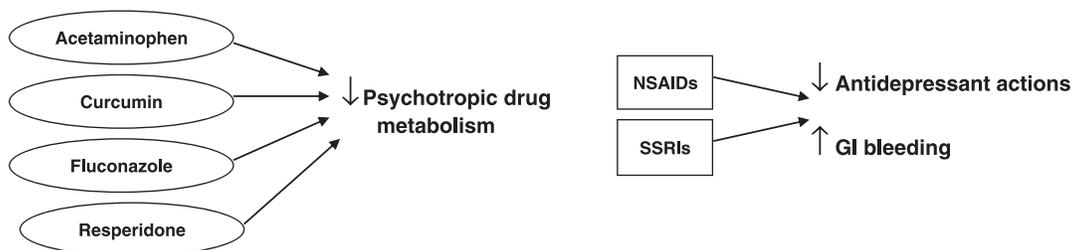
FIGURE 1. Diagrammatic representation of some of the most important interactions commonly seen among treatment of ASD. NSAIDs, nonsteroidal anti-inflammatory drugs.

indicate that one SSRI, citalopram, not only was not effective for children with ASD but may actually be detrimental.[36] These findings highlight the fact that psychotropic agents have different or worse adverse effects in children.[37]

METABOLISM

Autistic children seem to have decreased capacity to sulfoconjugate acetaminophen and therefore are unable to effectively metabolize particularly phenolic amines such as dopamine, tyramine, and serotonin.[38] Some authors even hypothesized that the increased rate of ASD may be at least partly due to acetaminophen[39] through decrease of glutathione levels (Fig. 1).[40] In view of this, parents have been shifting to ibuprofen. However, a recent study reported that using nonsteroidal anti-inflammatory drugs, such as ibuprofen, with SSRIs reduces the antidepressant effect of the latter[41] while increasing the risk of GI bleeding with SSRIs (Fig. 1).[42]

Taking multiple drugs increases the risk of adverse reactions, especially in children and neonates.[43] In a recent study of spontaneous reporting of adverse drug-drug interactions in Italy, the incidence was 9.8% for 2 drugs but increased to 88.3% for 8 drugs or more.[44] There is less information on drug-supplement interactions. However, it was reported that 33.4% of patients using antipsychotics also took traditional Chinese medicine concurrently; 7.2% of these patients had worse outcomes compared to 4.4% of those using antipsychotics alone.[45]

Risperidone is metabolized and can contribute to numerous drug interactions because it is metabolized by CYP3A4, the most common drug-metabolizing enzyme.[46] Many children have GI problems[47] and are given numerous medications that change the GI flora. In particular, they are often given antifungal medications,[16,17] such as fluconazole, which is a CYP3A inhibitor and can affect the metabolism of many drugs (Fig. 1).[48] Moreover, concurrent use of fluconazole and amitriptyline has resulted in syncope[49] and in serotonin toxicity presenting with delirium when given together with citalopram.[50]

POLYPHENOLS

Treatment approaches for ASD have featured the use of polyphenolic compounds such as anthocyanidins, curcumin, pycnogenol (pine bark extract), green tea, and ginseng extract. All of these are natural polyphenols present in plants, fruits, vegetables, and tea.[51] Oral administration of curcumin led to decreased intestinal P-glycoprotein and CYP3A and increased serum levels of their respective substrates celiprolol and midazolam (Fig. 1).[52] The main polyphenolic ingredients of grapefruit juice, the coumarins, also inhibit the liver enzyme CYP3A, affecting the metabolism and/or activation of numerous drugs and natural substances, whereas the main polyphenolic flavonoid naringin can inhibit the organic anion-transporting polypeptide family responsible for the transport of many hormones and drugs.[53]

This broad category of flavonoids also includes the subgroups of flavonols (quercetin) and flavones (luteolin).[51] Oral absorption and bioavailability of flavonoids are limited.[54] These substances have varying antioxidant and anti-inflammatory properties, mostly due to the degree of hydroxylation of their phenolic rings.[51] The main metabolism of a flavonol such as quercetin is by glucuronidation (quercetin-3′-glucuronide) and sulfation (quercetin-3′-sulfate).[55,56] Some children with ASD seem to be intolerant to polyphenols, presenting with increased hyperactivity. Not all phenolic compounds carry the same potential risk. For instance, pycnogenol from pine bark has 15 hydroxyl groups and naringin has 8 hydroxyl groups, as compared to quercetin's 5 hydroxyl groups and luteolin's 4 hydroxyl groups. More detailed information on interactions in general can be found elsewhere.[53,57]

LUTEOLIN AND QUERCETIN

Quercetin and its structural analog luteolin are generally safe.[58,59] In addition, a number of papers report protective effects of quercetin and luteolin both in the brain and liver.[60,61] For example, quercetin prevented liver toxicity induced by acetaminophen[62] and reduced haloperidol-induced dyskinesia in rodents.[63] Quercetin also prevented methylmercury-induced DNA damage,[64] whereas luteolin prevented mercury and thimerosal-induced inflammatory mediator release from immune cells.[65] Luteolin was recently shown to inhibit microglial activation and is also neuroprotective.[66–72] In fact, a luteolin analog was shown to mimic the activity of brain-derived neurotrophic factor.[73] A recent report also indicated that phenols in olive leaf extract can prevent blood-brain barrier disruption,[74] which has been proposed as a key pathogenetic factor in ASD.[18,75] Formulations containing luteolin in olive kernel extract are, therefore, likely not only to permit higher absorption of luteolin in the brain but also provide the additional benefit of blood-brain barrier protection.

Patients may still develop idiosyncratic reactions through activation of a unique immune cell, the mast cell, found in all tissues and responsible for allergic and inflammatory reactions.[76] The likelihood of idiosyncratic reactions may, therefore, be increased in the subgroup of patients with ASD who seem to have "allergic-like symptoms"[77] that involve mast cell activation by nonallergic triggers.[78]

Given the high percentage of children with ASD being treated with multiple pharmacologic and nonpharmacologic interventions, attention to interactions is a vital, but often overlooked, aspect of clinical management. Awareness of efficacy, safety, and unwanted interactions could increase the benefits of treatment and prevent adverse effects.

AUTHOR DISCLOSURE INFORMATION

patents 7,906,153 and 12/861,152 (allowed) for treatment of neuroinflammatory conditions, as well as US patent applications No. 12/534,571 and No. 13/009,282 for the diagnosis and treatment of ASD.

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