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Neuropsychiatric effects of medications for allergic diseases

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Abbreviations used

CNS: Central nervous system
OTC: Over-the-counter
PPA: Phenylpropanolamine

Adverse reactions to drugs and the perceptions associated with them influence prescribing patterns and undermine compliance. This concern gains significance in the treatment of chronic dis-

orders such as asthma for which successful management requires that patients take medications consistently over prolonged periods. Although there is general agreement about the physical side effects of asthma medications, neuropsychiatric manifestations have been a source of controversy.^{1,2} Disagreement exists over definitions of impairment and methods of assessment.³ The documentation of neuropsychiatric side effects is made further difficult because their onset may be delayed, they may persist beyond the discontinuation of the provoking medication, and they may be difficult to discriminate from the detrimental effects of chronic illness on mood and behavior.² Moreover, many patients may be taking several medications for the control of asthma and additional medications for the control of allergic rhinitis. Finally, the literature in this area consists largely of case reports and case reviews that rely on the patients' own accounts and may be subjective and inaccurate.³

THEOPHYLLINE

Numerous studies of theophylline side effects have been conducted with children, but few with adults. Theophylline has been widely reported to cause neuropsychiatric changes in children including impaired memory, motor skills, attention, and school adaptation.¹ Half of the parents of asthmatic children responded to a survey with reports that taking theophylline caused their children to become restless, hyperactive, or both.⁴

Recent evidence indicates that these reports have been exaggerated. Bender et al. evaluated psychologic side effects of theophylline in two studies, one open-label⁵ and one blinded.³ Both studies investigated children with asthma in placebo-controlled, randomized protocols with identical parent questionnaires and tests measuring attention, impulsivity, activity level, hand steadiness, memory, and self-reported mood. In the open-label study, children demonstrated improved attention on laboratory measures, although their parents noted conduct problems and hyperactivity, which they attributed to theophylline.⁵ In the blinded study, the children again demonstrated improved attention, along with slightly increased hand tremor and anxiety during the drug phase.³ However, this time the parents could not discriminate between the placebo and theophylline treatment conditions, a striking finding inasmuch as only children with a history of theophylline-induced psychologic side effects reported by their parents participated in this study.

In one investigation parents identified detrimental changes in behavior during the first week of theophylline therapy, but not in the second, leading the authors to conclude that these side effects were transient.⁶ Psychologic test scores failed to show any treatment-related differences, and parents were unable to observe behavior changes in other blinded studies in which standardized questionnaires were used.^{1,7} This absence is impressive, given the large number of dependent measures; for example, the study by Schlieper et al.⁷ assessed 21 psychologic variables from tests of memory, maze tracing, logic and analysis, perceptual motor speed, self-reported mood, and parent-reported behavior; none revealed significant theophylline or placebo treatment changes.

In most studies reporting theophylline-related behavior change, nonsignificant results greatly outnumbered significant findings. In some instances investigators appear to have overemphasized a single outcome.¹ There is little objective evidence that theophylline has a widespread adverse effect on children's mood and behavior, although subtle changes such as enhanced attention or memory^{1,3} and increased hand tremor and anxiety have been documented.³ In each case mean differences were small and not likely of clinical importance. The report that standardized scholastic achievement test scores of children taking theophylline for treatment of asthma are not different from those of their sibling controls should ease the concern over its effect on school performance.⁸

The results of studies of behavioral side effects in adults are similar to those of the larger body of research conducted in children. Theophylline was associated with improved verbal learning but decreased motor steadiness in both adults and adolescents with asthma.⁹ A study of normal adults, which avoided the potentially confounding effects of bronchodilation, reported no significant differences between theophylline and placebo on subjective or objective assessment of cognitive performance.¹⁰

CORTICOSTEROIDS

Concern over psychologic side effects of steroids is derived from numerous case reports of psychiatric disturbance in adults gathered over the past 40 years.² The largest of the case review studies is the Boston Collaborative Drug Surveillance Program.¹¹ Of 676 hospitalized patients who were treated with corticosteroids, 3.1% demonstrated acute psychiatric reactions. A dose-response relationship was revealed. Only 1.3% of patients re-

ceiving less than 40 mg of prednisone per day had such reactions compared with 18.4% of patients receiving more than 80 mg. Results from this and other case review studies have led to the following conclusions: (1) most severe psychiatric reactions can be avoided with prednisone doses lower than 40 mg/day; (2) a psychiatric history does not predispose an individual to steroid-induced psychiatric disturbance; (3) women may have an increased risk of side effects compared with men.¹

Three prospective studies of adult patients, in which a quasi-experimental design (no random assignment to treatment groups) was used, did not identify any psychologic change related to steroid therapy.² In the only experimental study in which random assignment was used, 9 of the 28 patients with systemic lupus erythematosus receiving prednisone (60 to 100 mg/day) with or without azathioprine had psychotic symptoms, in contrast to none of the 22 patients who did not receive corticosteroids.¹² The finding of psychosis in one third of steroid-treated patients is striking, although central nervous system (CNS) disturbances are a common complication of systemic lupus erythematosus, which was not well controlled in the prednisone-treated group.¹² Therefore the increased incidence of steroid-induced psychosis among these patients may be the result of their illness, a view supported by the authors' failure to encounter psychiatric disturbances in their patients receiving kidney transplants, who received higher doses of corticosteroids.¹²

In contrast to the adult literature dominated by case reviews, the pediatric literature consists primarily of controlled studies adhering to experimental design. These studies provide evidence of mood and memory changes that are associated with steroid treatment.² Initial case reports described either euphoria or depressive symptoms when children with rheumatic carditis or asthma were treated with steroids.² Later controlled studies of steroid side effects in children used objective tests of mood and behavior. Patients were found to be more tired, argumentative, sad, and irritable when receiving steroids than when receiving placebo and to manifest visual and verbal memory deficits on the day of steroid treatment but not 24 or 48 hours later.² Recent studies have confirmed changes in the affect of children treated with steroids. Two took advantage of the brief high-dose prednisone burst therapy commonly used for exacerbation of asthma.^{2, 13} The children, particularly those with a preexisting history of emotional problems, were more anxious and de-

pressed when receiving the higher doses of prednisone.^{2, 13}

The memory impediment attributed to steroid therapy in children is of limited duration. In a study of 39 asthmatic children treated with theophylline, 51 treated with theophylline and systemic steroids, and 30 nonasthmatic control subjects, verbal and visual memory were found to be compromised only in the steroid-treated group.² These findings were present on the day of steroid treatment but not 24 or 48 hours later.

Behavioral changes attributed to inhaled corticosteroids are not well documented, but the cases of two adults and six children with hyperactive, aggressive, and oppositional behavior have appeared in the literature.² Four cases involved patients 5 years old or younger, underscoring the importance of including young children in future investigations.

β-AGONISTS

There are several isolated reports in the literature of psychosis associated with the administration of oral β-agonists. Short-term CNS stimulation, increased pulse rate, and skeletal muscle tremor are common side effects of these medications, whether administered orally or by inhalation.¹⁴ In asthmatic children a fine motor tremor was noted, but completion of more complex perceptual motor tasks involving speed, dexterity, and visual motor control was not impeded after albuterol inhalation.¹⁴ In a 4-week study of adolescents and adults, inhaled albuterol did not impair verbal learning, visual perception, mental speed and efficiency, or attention.

ANTICHOLINERGIC DRUGS

Quaternary salts of atropine, such as ipratropium bromide or atropine methyl nitrate, administered by inhalation are not associated with psychologic side effects. On the other hand, anticholinergics taken orally may cause systemic disturbances and profound CNS reactions. Asthmador, a preparation no longer in use, contained two powdered herbs, *Atropa belladonna* and *Datura stramonium*, the active ingredients of which were atropine and scopolamine. This asthma medication was dispensed in several forms, all to be smoked. In the late 1960s a report of seven young male patients who ingested Asthmador instead of smoking it appeared; these patients manifested disorientation, impairment of memory and intellectual functioning, and visual hallucinations. They demonstrated clinical evidence of anticholinergic tox-

icity such as flushed face, dilated pupils, poor coordination, rapid pulse, dry mouth, and nausea. All mental symptoms disappeared within 4 to 12 hours.¹⁵

Cough and cold medicines taken orally by patients with allergic rhinitis commonly contain anticholinergics, as well as antihistamines, decongestants, and expectorants. After the 1985 ruling by the Food and Drug Administration that anticholinergics are not safe and effective for over-the-counter (OTC) distribution, these agents have been removed from all but one OTC remedy.¹⁶ However, numerous preparations available by prescription contain methscopolamine, atropine, hyoscymine, scopolamine, or homatropine. These combinations present a cause for concern.

Excessive doses of atropine may result in acute psychosis.¹⁷ A review of 212 cases of stramonium overdose reported visual hallucinations in 50% of cases, and disorientation, hyperactivity, combativeness, and amnesia in 10% to 21%.¹⁸ Even the use of mydriatic eye drops has been associated with auditory and visual hallucinations and amnesia.¹⁹

The literature documenting psychiatric reactions caused by anticholinergic agents is limited to case reports; however, several controlled studies have evaluated specific behavioral changes after the administration of atropine in the laboratory. Visual perception, reaction time, coordination, verbal memory, and motor steadiness showed impairment after the administration of atropine in normal male volunteers, with a greater deficit at a dose of 1.7 mg than at 0.85 mg.²⁰ Subsequently, no side effects were detected at a dose of 1.5 mg, but an impairment was documented on tests of visual discrimination, calculation, and memory when subjects received 3.0 mg and increased when the dose was raised to 6.0 mg. The subjects also reported dose-related symptoms that included nausea, confusion, blurred vision, restlessness, sleepiness, and feeling "high" that originated 1.5 hours after ingestion and disappeared 7 to 9 hours later.²¹

ANTIHISTAMINES

H₁ antihistamines have been reported to cause psychologic side effects including hallucinations, anxiety, psychosis, and catatonic stupor²²; however, their most widespread and serious drawback is sedation. Antihistamines can cause drowsiness in as many as 25% of adults, especially at high serum concentrations.²³ Second-generation H₁ antihistamines including astemizole, loratadine, and terfenadine do not cross the blood-brain barrier.²⁴ Numerous studies have shown that they are less likely to result in sedation or impairment of psy-

chomotor performance in adults.²⁵ In one study, adults treated with terfenadine demonstrated no compromise in coordination or alertness in contrast to those taking chlorpheniramine, clemastine, and promethazine.²⁵ Chlorpheniramine resulted in visual-motor impairment shortly after administration, and the performance deficits caused by clemastine and promethazine were more severe but appeared later.²⁵

It is important to note that patients frequently fail to recognize impairment caused by antihistamines, and the correlation between their own assessment and objective measures of sedation is poor.²⁶ In one study, subjects reported adverse effects despite the absence of treatment-related changes on tests of psychomotor skills,²⁷ whereas in another study, subjects reported no sedation, although impairment was demonstrated in the laboratory.²⁸

Limited available information indicates that children also experience side effects when taking antihistamines, but not when taking nonsedating antihistamines. In one study comparing terfenadine and placebo in 6- to 12-year-olds, no difference was found in the occurrence of side effects.²⁹ Unfortunately, a control group of children treated with classic antihistamines was not included, and no psychomotor tests were administered. In a recently published study of children with seasonal allergic rhinitis, those receiving diphenhydramine demonstrated impaired learning skills compared with children receiving loratadine or placebo.³⁰ One case report describes three preschool children in whom uncontrollable behavior and hallucinations developed after administration of triprolidine-pseudoephedrine,³¹ and another report describes three preschoolers with varicella-zoster infection who had visual and auditory hallucinations after the topical application of large amounts of diphenhydramine.³²

CNS disturbances may also occur after therapy with histamine-2 receptor blockers.³³ As of 1991, 88 cases had been reported in the medical literature, and 1296 cases were reported to the Food and Drug Administration.³³

SYMPATHOMIMETICS

Cough and cold remedies comprise a major portion of the OTC market. More than 150 of these preparations contain phenylpropanolamine (PPA), a sympathomimetic drug closely related to ephedrine (phenyl propanol methyl amine) and amphetamine (phenyl propane amine). In 1982, 412,000 pounds of PPA was produced in the United States.³⁴

PPA-associated psychosis was reported in three

patients who exhibited delusions, paranoia, auditory and visual hallucinations, confusion, and disorientation.³⁵ A subsequent review of 37 cases identified OTC combination products rather than PPA alone as the most likely causes of psychiatric side effects. Individuals with significant psychiatric history, children under the age of 6, and women post partum appeared to be at greater risk.³⁶ An interaction between PPA and caffeine has been linked with manic psychosis³⁷ and acute memory loss with nominal aphasia.³⁸ A report of 142 adverse drug reactions attributed to PPA includes acute hypertension, severe headaches, toxic encephalopathy, intracranial hemorrhages, seizures, and eight deaths. An overdose of PPA was taken in about one third of the cases.³⁹

Eighty percent of cases of adverse reactions to PPA that were reported to the Swedish Adverse Drug Reaction Committee involved patients under 15 years of age.⁴⁰ Five patients, four of them children, manifested acute psychosis, including profound confusion and visual hallucination; the remainder experienced restlessness, irritability, and sleep disturbance. Aggressiveness was noted, particularly in younger children. A 17-year-old boy was admitted to a mental hospital three times within a few months for treatment of acute mania-like psychosis, which was subsequently attributed to high doses of PPA and PPA with brompheniramine.⁴⁰

An excessive dose of another sympathomimetic agent, pseudoephedrine, has been reported to have precipitated a bipolar disorder in a 13-year-old girl.⁴¹ The participation of 9 of 74 children in a clinical trial of pseudoephedrine and triprolidine had to be terminated because of side effects that included irritability, dizziness, general malaise, and nightmares.⁴² Three children, aged 2.5 to 3.5 years, experienced severe visual hallucinations attributed to the same drug combination,³¹ and 50 more possible cases of CNS side effects were reported to the authors after the publication of these findings.⁴³

Toxic psychosis has been reported after excessive dosing with ephedrine.⁴⁴ This drug, closely related to pseudoephedrine and PPA, is still available in several combination asthma remedies.

DISCUSSION

Neuropsychiatric side effects, including sedation, psychosis, impaired learning and memory, disturbed affect, and behavioral disorders have been linked to medications used in the treatment of asthma and allergic rhinitis. In reviewing publications on this subject, greatest weight must be given to well-controlled, experimental studies such

as those addressing the use of theophylline and corticosteroids in children. Interpretation of the results is constrained by three problems.

First, the literature is comprised largely of case reports that document an association between a medication and an adverse reaction but do not confirm a cause-and-effect relationship.

Second, statistically significant differences in some measures of mood, memory, or attention may not be clinically relevant. As noted in the discussion of theophylline, cognitive changes that appear to be favorable and other significant treatment-related differences are quite small and are greatly outnumbered by nonsignificant comparisons. Thus the implications for the safe use of this drug by most patients are minimal.

Third, focusing on mean differences in psychologic test results may lead to the conclusion that all individuals are equally affected, when only a subgroup may experience serious reactions. In the case of corticosteroids, children with a history of emotional difficulty¹³ and women may be at increased risk.^{2, 12} These observations, however, have been drawn from relatively few cases, with suspected risk factors accounting for only a small portion of treatment variance. In the case of theophylline, increased sensitivity has been proposed in children under 7 years of age¹ and those with low IQ scores or attention or achievement problems,⁷ but evidence to support these hypotheses is limited, and a multivariate analysis showed that such susceptibility cannot be predicted on the basis of demographic or psychologic characteristics.³ Thus no subgroup likely to develop adverse psychologic reactions to either theophylline or corticosteroids has been conclusively identified.

Medicines for allergic rhinitis and those used for cough and colds constitute the largest group of drugs on the market.³⁴ These preparations are taken not only by patients with allergic disease but also by those with self-limiting respiratory symptoms. Many are available over the counter and are frequently taken without the supervision of physicians. They comprise a confusing array of combination antihistamines, decongestants, expectorants, and anticholinergic agents. This state is further complicated for patients with asthma who may be taking these preparations in addition to their prescribed regimen. The potential of these medications, alone or in combination, for producing neuropsychiatric side effects is inadequately recognized. Further investigation into the neuropsychiatric side effects of these drugs is needed to define those groups of patients who require closer monitoring.

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