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REVIEW OF THERAPEUTICS

Pharmacotherapeutic Considerations for Individuals with Down Syndrome

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Down syndrome (DS; trisomy 21) is the most common survivable disorder due to aneuploidy. Individuals with DS may experience multiple comorbid health problems including congenital heart defects, endocrine abnormalities, skin and dental problems, seizure disorders, leukemia, dementia, and obesity. These associated conditions may necessitate pharmacotherapeutic management with various drugs. The complex pathobiology of DS may alter drug disposition and drug response in some individuals. For example, reports have documented increased rates of adverse drug reactions in patients with DS treated for leukemia and dementia. Intellectual disability resulting from DS may impact adherence to medication regimens. In this review, we highlight literature focused on pharmacotherapy for individuals with DS. We discuss reports of altered drug disposition or response in patients with DS and explore social factors that may impact medication adherence in the DS setting. Enhanced monitoring during drug therapy in individuals with DS is justified based on reports of altered drug disposition, drug response, and other characteristics present in this population.

KEY WORDS Down syndrome, trisomy 21, pharmacotherapeutics, medication adherence, gene dosage effect, seizure disorder, leukemia, adverse drug reactions.

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Down syndrome (DS), also known as trisomy 21, is the most common survivable chromosomal disorder due to aneuploidy.¹ The incidence of DS in the United States is ~1 per 700 live births, and the worldwide incidence is ~1 per 1000 live births.¹ DS is caused by the presence of an additional whole or partial copy of chromosome 21 in affected individuals that results in genome-

wide imbalances with a range of phenotypic consequences.² Individuals with DS often exhibit associated disorders that contribute to elevated health care needs and financial costs.³ In spite of the high incidence of multiple adverse health conditions, the life expectancy of individuals with DS has increased to ~60 years of age.⁴ Individuals with DS will likely have increased health care needs as they age.⁵

The complex pathobiology of DS results in physical deficits and biochemical changes that can lead to multiple comorbid conditions. Gastrointestinal malformations such as duodenal stenosis and Hirschsprung disease are associated with DS.⁶ DS can impact immune responses, resulting in individuals being more susceptible to certain infections (e.g., upper respiratory tract infections).⁷ Celiac disease and other food intolerances are also more common in individuals with DS.^{8, 9} Congenital heart defects are common in those with DS, whereas the incidence of coronary artery disease (CAD) is lower than in

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subjects without DS.¹⁰ One study found that 9.9% of persons with DS older than 40 years died as a result of CAD.¹¹ A lower level of homocysteine in individuals with DS is thought to contribute to the reduced incidence of CAD; however, this has yet to be confirmed.¹² The frequency of congenital hypothyroidism is 28 times higher in individuals with DS in comparison with those without DS.¹³ Multiple skin conditions are also associated with DS and can lead to recurrent skin and soft tissue infections.¹⁴ DS is a leading cause of intellectual disability.¹⁵ Neurologic conditions such as seizure disorders and early-onset dementia are prevalent in the DS population. Children with DS are at an increased risk for hematologic disorders such as acute myeloid leukemia, acute lymphoblastic leukemia, and anemia.¹⁶ Obesity, dental problems, and apnea are also associated with DS.¹⁷

Although some physical deficits in DS may be corrected with surgery, medications are often used to manage various comorbid health conditions in individuals with DS. This results in high rates of medication use by those with DS.¹⁸ Unfortunately, there is often a lack of prospective research to make evidence-based recommendations for all DS-associated conditions and anomalies. Thus the treatment of comorbid conditions associated with DS can be a daunting task for health care providers and often requires multiple approaches. This concise review highlights the literature that focuses on pharmacotherapy for individuals with DS, indicates incidences of altered drug disposition or response, and justifies the need for further investigation of drug therapy in individuals with DS. This information may be relevant for health care professionals who manage patients with DS.

Literature Review

Published reports concerning medication use, adherence, disposition, and effect in subjects with DS were considered for this review. The PubMed and Ovid databases were used to search and identify the reports. These keywords were used: *Down syndrome, trisomy 21, pharmacotherapy, adverse drug reaction, drug treatment, pharmacokinetics, pharmacodynamics, and drug metabolism*. The search was performed from March 2016 through July 2016 and yielded primary research articles as well as other relevant reviews on related topics. The publication dates of reports used in this review spanned from 1981 to 2016.

Alterations in Drug Disposition and Drug Response

Dementia and Psychiatric Disorders

Individuals with DS have a greater risk of developing Alzheimer's-like dementia earlier in life compared with individuals without DS.¹⁹ Rivastigmine, galantamine, memantine, and donepezil have been used to treat Down syndrome-associated dementia (DSAD).²⁰ Donepezil has shown significant therapeutic efficacy in multiple reports. One small study showed improvement in dementia scores in subjects treated with donepezil during the 3- to 5-month time period ($p=0.03$). Subjects were treated with initial doses of donepezil 5 mg/day for 50 days, followed by 10 mg/day for 60 days.²¹ Other studies did not show significant improvement in subjects with DSAD who were treated with donepezil.²² Elevated frequencies of adverse effects from donepezil have been reported in subjects with DSAD.²³ For example, in two separate reports, a total of six individuals with DSAD developed gastrointestinal disturbances, altered mental status, or urinary incontinence following treatment with donepezil of varying duration (weeks to months).^{24, 25} A small group of 14 healthy subjects with DS did show higher donepezil plasma concentrations than a comparator group of 6 healthy subjects without DS.²⁵ In this study, the mean donepezil plasma concentration (while receiving donepezil 3–5 mg/day for 5 days) in subjects with DS was 17.9 and 28.2 ng/ml at doses of 3 mg/day and 5 mg/day, respectively, versus a mean plasma concentration of 7.8 and 17.7 ng/ml in the group of subjects without DS taking similar doses, respectively ($p<0.001$). The authors speculated that altered pharmacokinetics of donepezil could play a role in the increased incidence of adverse effects in subjects with DSAD and suggested that donepezil doses as low as 3 mg/day should be adequate for most patients with DSAD. It has been postulated that initiating treatment with donepezil at a lower dose and then titrating this dose, if necessary, may reduce the frequency of adverse effects in individuals with DSAD.²⁰ Rivastigmine, a cholinergic agent used for the treatment of mild to moderate dementia, has also been studied in subjects with DSAD. In one double-blind placebo-controlled trial in 22 children and adolescents with DS, rivastigmine treatment did not improve cognition, language, or overall function.²⁶ It was noted that subjects with DSAD tolerated rivastigmine therapy well.

Patients with DS can have high utilization rates of antidepressant and antipsychotic medications.¹⁸ These medications are given to some patients with DS and dementia to manage symptoms as well as other psychological disorders.²⁷ One case series explored the efficacy of administering antidepressants such as sertraline, fluoxetine, and citalopram to manage obsessive-compulsive disorder in four individuals with DS. It was reported to be an effective strategy.²⁸ One retrospective chart review suggested that the use of antidepressants (98% serotonin and serotonin-norepinephrine reuptake inhibitors) resulted in a 1.31-year delay in the onset of dementia ($p=0.038$) in individuals with DS.²⁹ The authors indicated the need for prospective studies to confirm their findings.

Seizure Disorders

Seizure disorders are associated with DS from childhood to adulthood.³⁰ Individuals with DS and seizure disorders are treated with traditional anticonvulsants. Therapy with multiple anticonvulsants such as carbamazepine, phenytoin, and valproic acid may be necessary for seizure control. It has been hypothesized that anticonvulsant polypharmacy may contribute to sudden unexpected death in some individuals with DS and epilepsy.³¹ Elevated homocysteine plasma levels and decreased folic acid plasma levels have been reported in individuals with DS following therapy with valproic acid.³² Hyperhomocysteinemia is a risk factor for cardiovascular disease, and supplementation with folic acid may be necessary for patients with DS who are receiving therapy with valproic acid.³² Reports of drug-induced seizures in those with DS are rare. One case report described a single patient with DS who developed seizures after treatment with the antihelminthic thiabendazole.³³ The author attributed the seizure to the person having DS; however, no follow-up study corroborated this observation.

Anticonvulsants such as carbamazepine and phenytoin, although necessary for seizure control in some patients, have the potential to further exacerbate other comorbid conditions and effects of DS. The potential exists for these agents and others to further reduce cognitive function in individuals with DS.³⁴ Carbamazepine also has the potential to exacerbate hypothyroidism in individuals with DS, and affected individuals may require increased doses of levothyroxine.³⁵ The potential for adverse

effects of pharmacotherapy with anticonvulsants in individuals with DS may necessitate gradual titration to effect and enhanced monitoring.³⁶

Respiratory Disorders

Respiratory disorders are common in people with DS. Impaired immune system function combined with respiratory tract defects make respiratory diseases a serious concern in individuals with DS.³⁷ Antibiotic therapy or inhaled bronchodilators may be needed to treat some respiratory problems related to DS.³⁸ A case series showed that the pharmacokinetics of the bronchodilator theophylline was altered in six infants with DS and apnea.³⁹ Specifically, it was reported that infants with DS exhibited reduced theophylline clearance. The observed mean clearance for the group with DS was 0.051 ± 0.035 L/kg/hour, whereas the expected range of clearance values for infants of similar ages was 0.089–0.102 L/kg/hour. In this study, no statistical comparisons were reported, and the authors noted that the use of concurrent medications could have impacted the observations. The authors speculated that the abnormal clearance of theophylline in the infants with DS could be related to altered levels of growth hormone that would in turn impact the expression of cytochrome P450 (CYP) drug-metabolizing enzymes. It should be noted that this was a retrospective case series. No prospective studies have yet substantiated these findings.

Hematologic Malignancies

Children with DS have an elevated risk of developing certain hematologic malignancies, such as acute myeloid leukemia.⁴⁰ These patients are generally treated with cytotoxic chemotherapy regimens that are often highly efficacious. Unfortunately, children with DS often display increased adverse effects from the chemotherapy.¹⁶ Potential contributing factors for this may include an underlying pro-oxidative state. Altered disposition of specific cytotoxic agents may play a role as well. Pediatric patients with DS displayed higher intracellular thioguanine metabolite concentrations when compared with those without DS.⁴¹ Elevated 42-hour methotrexate plasma concentrations were observed in subjects with DS.⁴¹ Most studies that considered the pharmacokinetics of cytotoxic chemotherapeutic agents in patients with DS postulated that altered cellular environments in the DS setting, rather

than pharmacokinetics, drive the differential response to chemotherapy agents.⁴¹ Few large prospective studies have investigated the impact of altered chemotherapy dosing in patients with DS; however, the reports that do exist often recommend treating hematologic malignancies with reduced doses of select cytotoxic chemotherapeutics, combined with close monitoring for toxicity.¹⁶ Pediatric patients with DS and leukemia who received prednisone with L-asparaginase displayed hyperglycemia at a higher rate compared with patients without DS.⁴² The authors suggested that this phenomenon was likely due to baseline insulin resistance in patients with DS.

Other Potential Pharmacotherapeutic Considerations

Besides biochemical alterations, DS can result in numerous physical anomalies that may impact pharmacotherapy. Individuals with DS and congenital hypothyroidism generally require supplementation with levothyroxine. One retrospective study that considered children with DS reported that therapy with low-dose levothyroxine (2.6 µg/kg/day) was adequate for hypothyroidism.¹³ The authors also recommended early screening for thyroid dysgenesis in children with DS and lifelong treatment with levothyroxine in those who are positive for the condition. The presence of uncorrected congenital heart defects necessitates antibiotic prophylaxis prior to many dental procedures.⁴³ Cardiac deficits may play a role in sudden unexpected death in individuals with DS and epilepsy who are taking multiple anticonvulsants, although this has not been confirmed in prospective studies.³¹ People with DS may require surgery to correct cardiac defects. The administration of anesthetic agents to individuals with DS prior to surgery requires special considerations. This is due to their unique airways and musculoskeletal and other systemic characteristics that may be present in subjects with DS.⁴⁴ In general, the requirements of narcotic-based therapy for the control of postoperative pain in patients with DS are similar to those for patients without DS. Retrospective studies have shown that therapeutic responses to opioid and nonopioid pain relievers after cardiac surgery were similar in both pediatric patients with and without DS.⁴⁵

Altered drug absorption in individuals with DS has yet to be thoroughly explored. Some comorbid conditions associated with DS and their respective treatments have been shown to impact

drug absorption and should be considered when assessing pharmacotherapeutic options in this patient population. Gastrointestinal malformations are more common in individuals with DS and can require surgery to correct.⁴⁶ Gastrointestinal surgery and disease have the potential to alter drug and nutrient absorption by altering pH, gastric emptying, and overall intestinal surface area.⁴⁷ Celiac disease present in those with DS may impact drug absorption; however, this has yet to be confirmed with large prospective studies.⁴⁸ The malabsorption of folic acid, iron, and cyanocobalamin associated with celiac disease may be a potentiating factor for anemia in some individuals with DS.⁴⁹

Social Considerations

DS is the leading cause of intellectual disability.¹ The degree of this impairment, as well as socioeconomic status, can vary among individuals and influence the daily needs and living arrangements of those with DS. These living arrangements (e.g., group home, semi-independent living, or family home) can potentially impact adherence to medications and vaccination guidelines. It has been reported that individuals with intellectual disabilities (including DS) living in a family home displayed higher rates of nonadherence to medication regimens compared with those in group homes.⁵⁰ Semi-independent living arrangements were also negative predictors of adherence in those with intellectual disabilities compared with those in a group home setting.⁵⁰ Guardians of children with DS may also influence therapy. One study reported that guardians of children with intellectual disabilities were more likely to refuse to vaccinate them.⁵¹

Individuals with DS have been shown to be at a higher risk for being socioeconomically disadvantaged, which may also impact adherence to treatment and vaccination guidelines.⁵² Poor adherence to guidelines may compromise the management of certain diseases in some individuals with DS. A study on children with DS found low levels of adherence to the American Academy of Pediatrics guidelines for thyroid screening.⁵³ It has been shown that subjects with developmental disabilities (including those with DS) from different racial or ethnic groups showed disparities in terms of adherence to antidiabetic medications.⁵⁴ Adherence to medication regimens is critical for treatment success. Poor medication adherence can contribute to

treatment failure, disease progression, and increased health care costs.⁵⁵ Few prospective studies have considered DS status as a factor potentially associated with medication adherence.

Discussion

Individuals with DS have distinctive biochemical and physical characteristics that can impact pharmacotherapy. To provide optimal care, it is important to recognize that persons with DS may respond differently to specific drug therapies. Based on the evidence available, the differential drug responses observed in DS appear to be largely driven by pharmacodynamic factors. Some drug-metabolizing enzymes, such as carbonyl reductase 1, are encoded in chromosome 21 and do exhibit differential expression in some tissues in individuals with DS.⁵⁶ Little evidence is available on differential CYP enzyme expression in persons with DS, and, as of yet, no evidence has linked altered drug disposition to the expression of CYP enzymes in individuals with DS. One report did indicate that single nucleotide polymorphisms in the *CYP17* and *CYP19* genes in those with DS may impact the bioavailability of endogenous estrogen, but therapeutic recommendations were not discussed.⁵⁷

Although evidence from well-powered studies is scarce, some reports suggest that those with DS can exhibit altered drug response in certain circumstances.¹⁶ Pediatric patients with DS and hematologic malignancies exemplify this notion; however, a large gap of knowledge remains.¹⁶ As individuals with DS live longer, they will likely encounter more age-related medical conditions. Medication utilization patterns, living conditions, and the status of caregivers are likely to shift with increasing age to include agents not well studied in those with DS, which may pose a risk to this group. Currently, there is scant research that considers pharmacotherapy in individuals with DS as well as the many chronic conditions they commonly face.⁵⁸ The level of information derived from studies investigating the efficacy and adverse effects of pharmacotherapy in those with DS is, for the most part, inadequate.

Multiple obstacles must be overcome to research the medication effects in individuals with DS. Preclinical studies can be encumbered by subject availability.⁵⁹ Many of the clinical studies that explored pharmacotherapy in subjects with DS were small, and others only

included results from a subgroup of subjects with DS. Clinical studies to ascertain the efficacy of psychotropic medications in subjects with DS may be challenging given the language and communication characteristics of individuals with DS.⁶⁰ The intellectual disability associated with DS, as well as inadequacies in living arrangements, may be predisposing factors for poor medication adherence. The reports on pharmacotherapy and individuals with DS suggest that monitoring is essential in this population, especially when considering that most medications have not been studied in relatively large groups of those with DS.

Conclusion

DS is associated with numerous health problems and high health care costs. Persons with DS display high medication utilization; however, few medications are studied in this at-risk population. Social conditions can impact medication utilization, but they remain largely uninvestigated in DS. Based on the information available, individuals with DS may require more intense monitoring for adverse effects, adherence, and treatment efficacy when being managed with medications. A more complete delineation of the factors that impact pharmacotherapy in the DS setting would contribute to the improvement of the clinical care of persons with DS.

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