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Pharmacotherapeutic Considerations for Individuals with Down Syndrome

Erik J. Hefti, PharmD, MS* and Javier G. Blanco, Clin. Biochem., PhD*

Department of Pharmaceutical Sciences, The School of Pharmacy and Pharmaceutical Sciences, The State University of New York at Buffalo, Buffalo, New York, United States of America

Abstract

Down syndrome (DS, trisomy 21) is the most common survivable 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 cases. 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 in DS. We discuss reports of altered drug disposition or response in cases 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.

Keywords

Down syndrome; Trisomy 21; Pharmacotherapeutics; Medication adherence; Gene dosage effect; Seizure disorder; leukemia; adverse drug reactions

Introduction

Down syndrome (DS), also known as trisomy 21, is the most common survivable chromosomal disorder. The prevalence of DS in the United States is approximately 1 per 700 live births and the worldwide incidence is estimated at 1 per 1000 live births¹ DS is caused by the presence of an additional whole or partial copy of the 21st chromosome in affected individuals, which results in genome-wide imbalances with a range of phenotypic consequences². Individuals with DS often exhibit associated disorders that contribute to elevated healthcare needs and financial costs³. In spite of the high incidence of multiple adverse health conditions, the life expectancy of individuals with DS has increased to approximately 60 years of age⁴. Individuals with DS will likely have increased healthcare

*Corresponding Author: Erik Hefti, PharmD, MS, Department of Pharmaceutical Sciences, The State University of New York at Buffalo, 471A Kapoor Hall, Buffalo, NY 14214, Telephone: 716-645-4812, erikheft@buffalo.edu, Javier G. Blanco, Clin. Biochem., PhD, Department of Pharmaceutical Sciences, The State University of New York at Buffalo, 470 Kapoor Hall, Buffalo, NY 14214, Telephone: 716-645-4820, Fax: 716-645-3693, jgblanco@buffalo.edu.

needs as they age⁵. 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 Hirschprung disease are associated with DS⁶. DS can impact immune responses, resulting in individuals being more susceptible to certain infections (e.g., infections in the upper respiratory tract)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, while the incidence of coronary artery disease (CAD) is lower than in subjects without DS¹⁰. One study found 9.9% of persons with DS over 40 years of age died as a result of CAD¹¹. Lower levels of homocysteine in DS is thought to contribute to the reduced incidence of CAD, however; this has yet to be confirmed¹². The frequency of congenital hypothyroidism is 28 times higher in cases with DS in comparison to those without DS¹³. Multiple skin conditions are also associated with DS and can lead to recurrent skin and soft tissue infections¹⁴. DS is a leading cause of intellectual disability¹⁵. 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 anemia¹⁶. Obesity, dental problems, and apnea are also associated with DS¹⁷.

While 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 drug utilization by those with DS¹⁸. 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 to healthcare providers and often requires multiple approaches. The purpose of this concise review is to highlight literature that focuses on pharmacotherapy in DS, indicate incidences of altered drug disposition or response, and justify the need for further investigation of drug therapy in DS. This information may be relevant for healthcare professionals that manage patients with DS.

Literature Analysis

Published reports concerning medication utilization, adherence, disposition, and effect in subjects with DS were considered for this review. The databases PubMed and OVID were utilized for searching and identifying the reports. The following keywords were used: “Down syndrome”, “trisomy 21”, “pharmacotherapy”, “adverse drug reaction”, “drug treatment”, “pharmacokinetics”, “pharmacodynamics”, and “drug metabolism”. This search took place 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 that were utilized in this review span from 1981 to 2016.

Alterations in Drug Disposition and Drug Response in DS

Dementia and Psychiatric Disorders

Individuals with DS have a greater risk of developing Alzheimer’s-like dementia earlier in life compared to individuals without DS¹⁹. 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 ($p = 0.03$). The subjects were treated with initial doses of 5 mg daily for 50 days, followed by 60 days of 10 mg daily of donepezil²¹. Other studies did not show significant improvement in subjects with DSAD who were treated with donepezil²². Elevated frequencies of adverse effects from donepezil have been reported in subjects with DSAD²³. For example, in two separate reports, a total of 6 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 plasma concentrations of donepezil than a comparator group of 6 healthy subjects without DS. In this study, the mean plasma concentration of donepezil (3 - 5 mg/day for 5 days) in subjects with DS was 17.9 ng/mL and 28.2 ng/mL versus a mean plasma concentration of 7.8 ng/mL 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 donepezil doses as low as 3 mg daily should be adequate for most patients with DSAD²⁵. It has been postulated that initiating treatment with donepezil at a lower dose and titrating may reduce the adverse effects in individuals with DSAD²⁰. 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 function²⁶. It was noted that subjects with DSAD tolerated rivastigmine therapy well and no pharmacokinetic parameters were reported.

Patients with DS can have high utilization rates of antidepressant and antipsychotic medications¹⁸. These medications are given to some with DS and dementia to manage symptoms, as well as other psychological disorders²⁷. One case series explored the efficacy of administering antidepressants such as sertraline, fluoxetine, and citalopram to manage obsessive compulsive disorder in 4 individuals with DS. It was reported to be an effective strategy²⁸. One retrospective chart review suggested that the utilization 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. The authors of the study indicated the need for prospective studies to confirm these findings²⁹.

Seizure Disorders

Seizure disorders are associated with DS from childhood to adulthood³⁰. 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 poly-pharmacy may contribute to sudden unexpected death in some people with DS and epilepsy³¹. Elevated plasma levels of homocysteine and decreased plasma levels of folic acid have been reported in individuals with DS following therapy with valproic acid³². 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 acid³². Reports on drug-induced seizures in

those with DS are rare. One case report described a single subject with DS who developed seizures after treatment with the antihelminthic thiabendazole. The author attributed the seizure to the subject having DS; however, no follow-up study corroborated this observation³³.

Anticonvulsants such as carbamazepine and phenytoin, while necessary for seizure control in some patients, have the potential to further exacerbate other comorbid conditions and effects of DS. There is the potential for these agents and others to further reduce cognitive function in individuals with DS³⁴. Further, carbamazepine has the potential to exacerbate hypothyroidism in DS, and affected individuals may require increased doses of levothyroxine³⁵. The potential for adverse effects of pharmacotherapy with anticonvulsants in individuals with DS may necessitate gradual titration to effect and enhanced monitoring³⁶.

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 DS³⁷. Antibiotic therapy or inhaled bronchodilators may be needed to treat some respiratory problems related with DS³⁸. A case report series showed that the pharmacokinetics of the bronchodilator theophylline was altered in 6 infants with DS and apnea. Specifically, it was reported that infant patients with DS exhibited reduced theophylline clearance. The observed mean clearance for the group with DS was 0.051 ± 0.035 L/kg/hr whereas the expected range of clearance values for infants of similar ages was 0.089 - 0.102 L/kg/hr. In this study, no statistical comparisons were reported, and the authors noted that the use of concurrent medications could have impacted the observations³⁹. The authors speculated that the abnormal clearance of theophylline in the infants with DS could be related to altered levels of growth hormone which would in turn impact the expression of cytochrome P450 drug metabolizing enzymes. This was a retrospective case series and no prospective studies have yet substantiated these findings.

Hematological Malignancies

Children with DS have an elevated risk of developing certain hematological malignancies, such as acute myeloid leukemia⁴⁰. These patients are generally treated with cytotoxic chemotherapy regimens, which are often highly efficacious. Unfortunately, children with DS often display increased adverse effects from the chemotherapy¹⁶. 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 subjects with DS displayed higher intracellular thioguanine metabolite concentrations when compared to subjects without DS. Methotrexate had elevated 42-hour plasma concentrations in subjects with DS. Most studies that considered the pharmacokinetics of cytotoxic chemotherapeutic agents in patients with DS postulated that altered cellular environments in the DS setting drive the differential response to chemotherapy agents rather than pharmacokinetics⁴¹. There are few large prospective reports that investigated the impact of altered chemotherapy dosing in patients with DS; however, the reports that do exist often recommend treating hematological malignancies with reduced doses of select cytotoxic chemotherapeutics combined with close

monitoring for toxicity¹⁶. Pediatric patients with DS and leukemia receiving prednisone with L-asparaginase displayed hyperglycemia at a higher rate compared to patients without DS. The authors suggested that this phenomenon was likely due to baseline insulin resistance in patients with DS⁴².

Other Potential Pharmacotherapeutic Considerations in DS

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. 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 condition¹³. The presence of uncorrected congenital heart defects necessitates antibiotic prophylaxis prior to many dental procedures⁴³. Cardiac deficits may play a role in sudden unexpected death in individuals with DS and epilepsy that are taking multiple anticonvulsants, although this has not been confirmed in prospective studies³¹. People with DS may require surgery to correct cardiac. The administration of anesthetic agents to individuals with DS prior to surgery requires special considerations. This is due to the unique airway, musculoskeletal, and other systemic characteristics that may be present in subjects with DS⁴⁴. In general, the requirements of narcotic-based therapy for the control of post-operative pain in patients with DS are similar to those for patients without DS. Retrospective studies have shown that therapeutic responses to opioid and non-opioid pain relievers after cardiac surgery were similar in pediatric patients with and without DS⁴⁵.

Altered drug absorption in 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 DS and can require surgery to correct. Gastrointestinal surgery and disease have the potential to alter drug and nutrient absorption by altering pH, gastric emptying, and overall intestinal surface area⁴⁶. Celiac disease present in those with DS may impact drug absorption, however; this has yet to be confirmed with large, prospective studies⁴⁷. The malabsorption of folic acid, iron, and cyanocobalamin associated with Celiac disease may be a potentiating factor for anemia in some individuals with DS⁴⁸.

Social Considerations in DS

DS is the leading cause of intellectual disability¹. The degree of this impairment, as well as socioeconomic status, can vary among individuals and can 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 medication adherence. It has been reported that individuals with intellectual disabilities (including DS) living in a family home displayed higher rates of non-adherence to medication regimens when compared to group homes. Semi-independent living arrangements were also negative predictors of adherence in those with intellectual disabilities when compared to a group home setting⁴⁹. 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 them⁵⁰.

Individuals with DS had been shown to be at a higher risk for being socioeconomically disadvantaged, which may also impact adherence to treatment and vaccination guidelines⁵¹. Poor adherence to guidelines may compromise the management of certain diseases in some cases with DS. A study on children with DS found low levels of adherence to the American Academy of Pediatric guidelines for thyroid screening⁵². It has been shown that subjects with developmental disabilities (including those with DS) from different racial/ethnic groups showed disparities in terms of adherence to anti-diabetic medication⁵³. Adherence to medication regimens is critical for treatment success. Poor medication adherence can contribute to treatment failure, disease progression, and increased healthcare costs⁵⁴. There are few prospective studies that considered DS status as a factor potentially associated to medication adherence.

Discussion

Individuals with DS have unique biochemical and physical characteristics that can impact pharmacotherapy. In order to provide optimal care, it is important to recognize that subjects 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 (CBR1), are encoded in chromosome 21 and do exhibit differential expression in some tissues from subjects with DS⁵⁵. There is little evidence on differential CYP450 enzyme expression in DS, and there is no evidence linking altered drug disposition to the expression of CYP450 enzymes in DS as of yet. One report did indicate that single nucleotide polymorphisms in the *CYP17* and *CYP19* genes in subjects with DS may impact on the bioavailability of endogenous estrogen, but therapeutic recommendations were not discussed⁵⁶.

Although evidence from well powered studies is scarce, some reports suggest that those with DS can exhibit altered drug response in certain circumstances. Pediatric patients with DS and hematological malignancies exemplify this notion; however, a large gap of knowledge remains. 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 subjects with DS, which may pose a risk to this group. Currently, there is scant research that considers pharmacotherapy in subjects with DS and many chronic conditions they commonly face⁵⁷. The level of information derived from studies investigating efficacy and adverse effects of pharmacotherapy in subjects with DS is, for the most part, inadequate.

There are multiple obstacles for researching medication effects in individuals with DS. Pre-clinical studies can be encumbered by subject or sample availability⁵⁸. Many of the clinical studies that explore pharmacotherapy in subjects with DS are small, and others only include results from a subgroup of subjects with DS in the study or trial. 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 DS⁵⁹. 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 DS do suggest that monitoring is essential in this population, especially when considering that most medications have not been studied in relatively large groups of individuals with DS.

DS is associated with numerous health problems and high healthcare 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 improve the clinical care of people with DS.

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References

1. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Mental retardation and developmental disabilities research reviews*. 2007; 3:221–7.
2. Hook EB. Rates of chromosome abnormalities at different maternal ages. *Obstetrics and gynecology*. 1981; 3:282–5.
3. Boulet SL, Molinari NA, Grosse SD, Honein MA, Correa-Villasenor A. Health care expenditures for infants and young children with Down syndrome in a privately insured population. *The Journal of pediatrics*. 2008; 2:241–6.
4. Esbensen AJ. Health conditions associated with aging and end of life of adults with Down syndrome. *International review of research in mental retardation*. 2010; C:107–26.
5. Bittles AH, Glasson EJ. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Developmental Medicine & Child Neurology*. 2004; 4:282–86.
6. Stoll C, Dott B, Alembik Y, Roth M-P. Associated congenital anomalies among cases with Down syndrome. *European journal of medical genetics*. 2015; 12:674–80.
7. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clinical and Experimental Immunology*. 2011; 1:9–16.
8. Bade M, Rammeloo E, Hermans J, de Vries LA, de Graaf E, Mearin M. Symptoms of disease and food allergy in children with Down syndrome. *Nederlands tijdschrift voor geneeskunde*. 1995; 33:1680–84.
9. Carnicer J, Farré C, Varea V, Vilar P, Moreno J, Artigas J. Prevalence of coeliac disease in Down's syndrome. *European journal of gastroenterology & hepatology*. 2001; 3:263–67.
10. Raina T, McGrath E, Gunn J. Myocardial infarction in a patient with Down syndrome: a case report and review of the literature. *Clinical cardiology*. 2011; 2:87–89.
11. Bittles AH, Bower C, Hussain R, Glasson EJ. The four ages of Down syndrome. *The European Journal of Public Health*. 2007; 2:221–25.
12. Vis J, Duffels M, Winter M, et al. Down syndrome: a cardiovascular perspective. *J Intell Disabil Res*. 2009; 5:419–25.

13. Cebeci AN, Güven A, Yıldız M. Profile of hypothyroidism in Down's syndrome. *Journal of Clinical Research in Pediatric Endocrinology*. 2013; 2:116–20.
14. Barankin B, Guenther L. Dermatological manifestations of Down's syndrome. *Journal of Cutaneous Medicine and Surgery: Incorporating Medical and Surgical Dermatology*. 2001; 4:289–93.
15. Pulsifer MB. The neuropsychology of mental retardation. *J Int Neuropsychol Soc*. 1996; 2:159–76. [PubMed: 9375201]
16. Hefti E, Blanco JG. Anthracycline-related cardiotoxicity in patients with acute myeloid leukemia and Down syndrome: a literature review. *Cardiovascular toxicology*. 2016; 1:5–13.
17. Henderson A, Lynch SA, Wilkinson S, Hunter M. Adults with Down's syndrome: the prevalence of complications and health care in the community. *Br J Gen Pract*. 2007; 534:50–5.
18. Kerins G, Petrovic K, Bruder M, Gruman C. Medical conditions and medication use in adults with Down syndrome: a descriptive analysis. *Down Syndrome Research and Practice*. 2008; 2:141–47.
19. Visser FE, Aldenkamp AP, van Huffelen AC, Kuilman M, Overweg J, van Wijk J. Prospective study of the prevalence of Alzheimer-type dementia in institutionalized individuals with Down syndrome. *American journal of mental retardation : AJMR*. 1997; 4:400–12.
20. Prasher VP. Review of donepezil, rivastigmine, galantamine and memantine for the treatment of dementia in Alzheimer's disease in adults with Down syndrome: implications for the intellectual disability population. *International journal of geriatric psychiatry*. 2004; 6:509–15.
21. Lott IT, Osann K, Doran E, Nelson L. Down syndrome and Alzheimer disease: response to donepezil. *Archives of neurology*. 2002; 7:1133–6.
22. Mohan M, Carpenter PK, Bennett C. Donepezil for dementia in people with Down syndrome. *Cochrane Database Syst Rev*. 2009; 1 CD007178.
23. Hemingway-Eltomey JM, Lerner AJ. Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. *The American journal of psychiatry*. 1999; 9:1470.
24. Cipriani G, Bianchetti A, Trabucchi M. Donepezil use in the treatment of dementia associated with Down syndrome. *Archives of neurology*. 2003; 2:292–92.
25. Kondoh T, Nakashima M, Sasaki H, Moriuchi H. Pharmacokinetics of donepezil in Down syndrome. *The Annals of pharmacotherapy*. 2005; 3:572–3.
26. Spiridigliozzi GA, Hart SJ, Heller JH, et al. Safety and efficacy of rivastigmine in children with Down syndrome: A double blind placebo controlled trial. *Am J Med Genet A*. 2016; 6:1545–55.
27. Coppus A, Evenhuis H, Verberne GJ, et al. Dementia and mortality in persons with Down's syndrome. *J Intell Disabil Res*. 2006; 10:768–77.
28. Sutor B, Hansen M, Black J. Obsessive compulsive disorder treatment in patients with Down syndrome: a case series. *Down Syndrome Research and Practice*. 2006; 1:1–3.
29. Tsiouris JA, Patti PJ, Flory MJ. Effects of antidepressants on longevity and dementia onset among adults with Down syndrome: a retrospective study. *The Journal of clinical psychiatry*. 2014; 7:731–37.
30. Menendez M. Down syndrome, Alzheimer's disease and seizures. *Brain Dev*. 2005; 4:246–52.
31. Scorza CA, Scorza FA, Arida RM, Cavalheiro EA. Sudden unexpected death in people with down syndrome and epilepsy: another piece in this complicated puzzle. *Clinics*. 2011; 5:719–20.
32. Siniscalchi A, De Sarro G, Loizzo S, Gallelli L. High plasma homocysteine and low serum folate levels induced by antiepileptic drugs in Down syndrome. *Journal on Developmental Disabilities*. 2012; 2:70–76.
33. Tchao P, Templeton T. Thiabendazole-associated grand mal seizures in a patient with Down syndrome. *The Journal of pediatrics*. 1983; 2:317–8.
34. Lott IT, Doran E, Nguyen VQ, Tournay A, Movsesyan N, Gillen DL. Down syndrome and dementia: seizures and cognitive decline. *Journal of Alzheimer's Disease*. 2012; 1:177–85.
35. Badiu C, Verzea S, Picu M, Pencea C. Autoimmunity puzzle in Down syndrome. *Down Syndrome Research and Practice*. 2010; 2:98–102.
36. Solaro C, Uccelli MM, Mancardi G. A patient with multiple sclerosis and Down's syndrome with a rare paroxysmal symptom at onset. *European Journal of Neurology*. 1999; 4:505–07.

37. Pothos M. Aspiration: a common cause of respiratory problems in Down syndrome children. *Pediatric research*. 1999; 4(Part 2 of 2):130A–30A.
38. Doul I. Respiratory disorders in Down's syndrome: overview with diagnostic and treatment options. *Down's Syndrome Medical Interest Group*. 2002
39. Stowe CD, Phelps SJ. Altered clearance of theophylline in children with Down syndrome: a case series. *Journal of clinical pharmacology*. 1999; 4:359–65.
40. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet*. 2000; 9199:165–9.
41. Hefti E, Blanco JG. Pharmacokinetics of chemotherapeutic drugs in pediatric patients with Down syndrome and leukemia. *Journal of pediatric hematology/oncology*. 2016; 4:283–7.
42. Pui CH, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. *The Journal of pediatrics*. 1981; 1:46–50.
43. Abanto J, Ciamponi AL, Francischini E, Murakami C, de Rezende NPM, Gallottini M. Medical problems and oral care of patients with Down syndrome: a literature review. *Special Care in Dentistry*. 2011; 6:197–203.
44. Meitzner MC, Skurnowicz JA. Anesthetic considerations for patients with Down syndrome. *AANA J*. 2005; 2:103–7.
45. Van Driest SL, Shah A, Marshall MD, et al. Opioid use after cardiac surgery in children with Down syndrome. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2013; 9:862–8.
46. Gubbins PO, Bertch KE. Drug absorption in gastrointestinal disease and surgery. *Clinical pharmacokinetics*. 1991; 6:431–47.
47. Tran TH, Smith C, Mangione RA. Drug absorption in celiac disease. *American Journal of Health-System Pharmacy*. 2013; 24
48. Sala Castellví P, Llorens Jové ME, Ducet Vilardell P, et al. Anemia and celiac disease in a patient with Down syndrome. *International Medical Review on Down Syndrome*. 2008; 1:8–11.
49. Hom CL, Touchette P, Nguyen V, et al. The relationship between living arrangement and adherence to antiepileptic medications among individuals with developmental disabilities. *J Intellect Disabil Res*. 2015; 1:48–54.
50. Remes O, Smith LM, Alvarado-Llano BE, Colley L, Lévesque LE. Individual- and Regional-level determinants of Human Papillomavirus (HPV) vaccine refusal: the Ontario Grade 8 HPV vaccine cohort study. *BMC Public Health*. 2014; 1:1–9.
51. Williams IT, Milton JD, Farrell JB, Graham NM. Interaction of socioeconomic status and provider practices as predictors of immunization coverage in Virginia children. *Pediatrics*. 1995; 3:439–46.
52. Fergeson MA, Mulvihill JJ, Schaefer GB, et al. Low adherence to national guidelines for thyroid screening in Down syndrome. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2009; 7:548–51.
53. Patel I, Erickson SR, Caldwell CH, et al. Predictors of medication adherence and persistence in Medicaid enrollees with developmental disabilities and type 2 diabetes. *Res Social Adm Pharm*. 2016; 4:592–603.
54. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman medical journal*. 2011; 3:155–59.
55. Kalabus JL, Sanborn CC, Jamil RG, Cheng Q, Blanco JG. Expression of the anthracycline-metabolizing enzyme carbonyl reductase 1 in hearts from donors with Down syndrome. *Drug metabolism and disposition: the biological fate of chemicals*. 2010; 12:2096–9.
56. Chace C, Pang D, Weng C, et al. Variants in CYP17 and CYP19 Cytochrome P450 genes are associated with onset of Alzheimer's disease in women with Down syndrome. *Journal of Alzheimer's Disease*. 2012; 3:601–12.
57. Stores G, Stores R. Sleep disorders and their clinical significance in children with Down syndrome. *Developmental Medicine & Child Neurology*. 2013; 2:126–30.
58. Oster-Granite ML, Parisi MA, Abbeduto L, et al. Down syndrome: national conference on patient registries, research databases, and biobanks. *Molecular genetics and metabolism*. 2011; 1-2:13–22.

59. Martin GE, Klusek J, Estigarribia B, Roberts JE. Language characteristics of individuals with Down syndrome. *Top Lang Disord*. 2009; 2:112–32.