

In Brief

Among patients with type 1 or type 2 diabetes, depression is one of the most commonly occurring comorbid conditions. A dual diagnosis of depression and diabetes has been linked to poor adherence and decreased daily diabetes self-care and often leads to suboptimal metabolic control and increased diabetes-related complications. Pediatric diabetes clinicians are in a unique position to identify behavior changes over time and provide early identification and preventive intervention for children and adolescents at risk for depression. This article provides an overview of the differential diagnosis process that pediatric clinicians face and practical advice for providers when evaluating and addressing depressive symptoms during routine diabetes clinic visits.

Screening and Identification of Children and Adolescents at Risk for Depression During a Diabetes Clinic Visit

Maureen Monaghan, PhD, Chandra Singh, BS, Randi Streisand, PhD, CDE, and Fran R. Cogen, MD, CDE

Diabetes is one of the fastest growing public health concerns, with rates of diagnosis of type 1 and type 2 diabetes on the rise, particularly among young children.^{1,2} A diagnosis of a chronic illness such as diabetes is a significant risk factor for a number of related diagnoses, including medical comorbidities such as metabolic syndrome or autoimmune disorders and psychosocial concerns such as mood disorders.³

Among patients with type 1 or type 2 diabetes, depression is one of the most commonly occurring comorbid conditions, with estimates suggesting that 12–18% of children and adolescents with diabetes report clinically significant symptoms of depression.^{4–7} Currently, only half of all adolescents with depression are identified

and diagnosed before adulthood.⁸ Pediatricians and pediatric diabetes clinicians are in a unique position to identify early symptoms of depression and provide resources for treatment. Thus, identification and treatment of depression can be a crucial part of medical management of diabetes.

The majority of research exploring diabetes and depression has been conducted in adult subjects. Among adults with diabetes, rates of occurrence of depression are similar to the rates evident in adolescents, with ~12–15% of adults reporting clinically significant symptoms of depression at any given time. Using samples of predominantly type 2 diabetic patients, researchers estimate that a diagnosis of diabetes doubles the risk for depression in

adults.⁹ Factors related to the increased risk for depression among adults with diabetes include a greater number of medical comorbidities, female sex, younger age, and higher A1C level.^{3,10} Depression can also affect the course of diabetes treatment; patients who are dually diagnosed with depression and diabetes report increased complications related to diabetes, a higher perceived diabetes burden,¹¹ poorer adherence, and greater utilization of health care resources.¹²

Although less is known about depression and diabetes in children and adolescents, researchers are beginning to identify risk factors associated with the development of depression in young people with diabetes. Kovacs et al.¹³ examined prospective data from 92 young people from the time of diagnosis and found that, by the age of 20 years, 47.6% met diagnostic criteria for psychiatric comorbidity at some point during the 10-year period of study, with depression having the highest prevalence rate in this sample (27%). Hood⁴ found that depression was more likely in females with less frequent self-monitoring of blood glucose, poorer metabolic control, higher reported diabetes conflict, and higher perceived diabetes burden. The SEARCH study,⁷ a nationwide diabetes study enrolling 2,672 young people, found that females had higher mean depression scores than males, and males with type 2 diabetes were at greater risk for depressed mood than males with type 1 diabetes.

Although researchers have identified characteristics within a diabetes population that increase the risk for depression, current adolescent research is mixed when comparing rates of depression among youth with diabetes and among the general adolescent population.¹⁴ Therefore, a diagnosis of diabetes alone may not be sufficient for increased incidence of a depressive disorder.¹⁵ However, screening for depressive symptoms should be an integral part of diabetes care, given the occurrence of depression in the general adolescent population (estimates of up to 18%)¹⁶ and the potential associations of depression and diabetes with poor adherence to daily self-care and poor health outcomes.

One of the most significant concerns of the dual diagnosis of depression and diabetes is the association between depression and an increased risk of nonadherence, lead-

ing to suboptimal metabolic control and diabetes-related complications. Stewart et al.¹⁷ found that diabetic ketoacidosis (DKA) was twice as likely in children who reported clinically significant depressive symptoms. Similarly, Rewers et al.¹⁸ found that the presence of a psychiatric disorder, including depression, led to an increased risk for DKA and severe hypoglycemia because of less frequent blood glucose checks, increased variability in diet, and disrupted sleep/wake patterns. Lustman et al.¹⁹ hypothesized that a bidirectional physiological relationship may exist, with poor metabolic control leading to dysphoria, and dysphoria resulting in less attention to diabetes care with ultimately poorer metabolic control.

Despite the clear increased risk of depression in youth diagnosed with diabetes, many adolescents and young adults are not quickly identified as experiencing symptoms of depression.²⁰ Because diabetes teams typically see adolescents three to four times per year and routinely assess medical and family factors related to diabetes management, they are in a unique position to screen adolescents for depression and refer at-risk patients for further evaluation and treatment. Routine in-office screening for depression is an important part of a proactive system to identify patients at risk for complications and provide appropriate specialty referrals.²¹

However, identification of depression on the part of pediatric diabetes clinicians requires careful attention and skill, and time constraints of clinic visits may contribute to a missed diagnosis. Furthermore, the relationship among diabetes care, depression, and patient-reported physical and emotional symptoms is complex, and pediatric clinicians often must rule out a number of diagnoses that may mirror symptoms of a mood disorder in children and adolescents, including hypothyroidism,²² celiac disease,²³ sleep apnea,²⁴ and vitamin D deficiency.²⁵

The following two case studies highlight the complexity of routine 20- to 30-minute diabetes clinic visits with a physician and certified diabetes educator and serve to underscore the difficulty in clinical decision-making.

Case Study 1: J.A.

J.A. is an 11-year-old African-American boy who was diagnosed

with type 2 diabetes ~ 14 months ago by his family practitioner during a routine sports physical. Family history is significant for type 2 diabetes and cardiac disease. At the time of diagnosis, J.A.'s BMI was greater than the 99th percentile, and his fasting glucose level was 300 mg/dl, with an A1C of 12.3%.

After diagnosis, his family practitioner referred J.A. to an adult endocrinologist for care; however, after a 6-month course of oral medication, J.A.'s parents expressed concern about his continued erratic blood glucose levels and difficulty adhering to behavioral recommendations. His parents requested a consultation with a pediatric endocrinologist for guidance related to J.A.'s current diabetes regimen and information about the impact of diabetes management on J.A.'s mood and behavior. At the time of consultation, J.A. was prescribed metformin, 1,000 mg twice daily. Table 1 shows his physical exam and laboratory results.

Upon interview, J.A. presented as a quiet, polite pre-adolescent boy. He avoided eye contact and often looked at the floor when speaking. J.A.'s parents reported concerns about inconsistent blood glucose monitoring, frequent high blood glucose levels, decreased interest in activities, increased fatigue, increased appetite, and frequent school absences. J.A. agreed with his parents' concerns and became tearful when asked about his blood glucose monitoring frequency. He reported feeling tired all of the time and that he just "doesn't want to do anything."

His parents noted that this withdrawn behavior began after he was cut from the county football team in the fall and, although J.A. denies it, they worry that he is currently being teased at school for being overweight. J.A.'s grades had also declined during this school year, and his teachers have noted that he falls asleep in class and does not participate in class discussions.

Based on the information presented, major differential diagnoses under consideration are:

- Hyperglycemia
- Hypothyroidism
- Sleep apnea
- Major depressive disorder (MDD)
- Family dysfunction
- Peer victimization

Table 1. Physical Exam Data from Case Study 1 and Case Study 2

	Case Study 1: J.A.	Case Study 2: S.C.
General observations	Obese, normally developing pre-adolescent boy	Thin, normally developing adolescent girl
Vital signs		
Height	5'2"	5'4"
Weight (lb)	176	114
Blood pressure (mmHg)	122/83	110/70
Pulse (bpm)	95	68
Physical exam		
Skin	Acanthosis nigricans on neck and axillae	Normal skin pigmentation, no callosus formations on fingertips
Thyroid	Palpable smooth thyroid without nodules	Palpable smooth thyroid without nodules
Abdomen	Protuberant with striae, active bowel sounds	Normal with active bowel sounds
Pubertal Development	Tanner stage 2	Tanner stage 5
Diabetes management		
Average blood glucose checks/day	0.83	4.2
Average blood glucose: breakfast (mg/dl)	232	124
Average blood glucose: lunch (mg/dl)	N/A	198
Average blood glucose: dinner (mg/dl)	253	207
Average blood glucose: bedtime (mg/dl)	N/A	155
Initial laboratory results*		
A1C (%)	10.3 (normal 3.4–6.1)	8.1 (normal 3.4–6.1)
Estimated average glucose (mg/dl)	247.16	185.12
Blood urea nitrogen (mg/dl)	10 (normal 7–18)	N/A
Creatinine	0.8 (normal 0.6–1.3)	N/A
Aspartate/alanine aminotransferase (unit/l)	20/32 (normal 15–37/30–65)	N/A
Cholesterol (mg/dl)	190 (normal < 200)	N/A
Follow-up laboratory results*		
TSH (μ U/ml)	1.3 (normal 0.34–4.82)	0.98 (normal 0.34–4.82)
First morning cortisol (μ g/dl)	N/A	18 (normal 5–25)
tTG (U/ml)	N/A	100 (normal < 4.0)
Adrenal antibodies	N/A	Negative (normal)
Serum HCG	N/A	Negative (normal)

*Normal values based on normal ranges reported by a large mid-Atlantic children's hospital

At the conclusion of this clinic visit, it was recommended that J.A. increase his blood glucose monitoring to at least twice per day, obtaining one fasting measurement and one 2 hours after a meal at different times

throughout the week to obtain a more detailed blood glucose profile. His oral medication was maintained pending additional data. When questioned about symptoms of sleep apnea, his parents denied that J.A. snores. The

clinician suggested that they contact his primary care physician if they witnessed snoring or pauses in breathing during sleep. Symptoms of hyperglycemia, hypothyroidism, and a possible overlap with depressive symp-

toms were discussed and, pending thyroid-stimulating hormone (TSH) test results, his parents were given the contact information of the diabetes team psychologist to find out more information about treatment options and psychosocial providers in their area. He was referred for additional lab work to rule out hypothyroidism.

Follow-up lab evaluation revealed a TSH of 1.3 $\mu\text{U/ml}$ (normal = 0.34–4.82 $\mu\text{U/ml}$). J.A. was subsequently evaluated by the diabetes team psychologist, who confirmed the medical team's initial assessment of MDD, Moderate, Single Episode. He was referred to a licensed clinical social worker in his area and was followed bimonthly for counseling with parent-reported improved affect, increased energy, and a 3% weight loss.

Case Study 2: S.C.

S.C. is a 17-year-old Caucasian girl who was diagnosed with type 1 diabetes at 8 years of age. Family history is significant for a maternal uncle with type 1 diabetes and a maternal aunt with ulcerative colitis. Since diagnosis, she has been followed by a pediatric endocrinology clinic at a large children's hospital. She has been managing diabetes using insulin pump therapy for the past 5 years, and her A1C consistently ranges from 6.5 to 8.5%. During the past year, she has checked her blood glucose levels three to eight times per day, averaging 4.8 checks per day.

Over the course of the past three visits, S.C. has had no significant weight fluctuations but has complained of intermittent abdominal pain, headaches, unpredictable menstrual periods, and occasional diarrhea. Her mother has also raised concerns of increased school absences secondary to vague abdominal pain, increased moodiness, and anxiety related to college decisions. S.C. was seen for a routine diabetes visit. Table 1 shows her physical exam and laboratory results.

Upon interview, S.C. presented as a bright, anxious adolescent girl. She reported feeling worried about her college applications and her current social relationships because she had recently broken up with her boyfriend. She continued to complain of stomach pain and indicated being worried that she has an ulcer. S.C.'s mother reported increased conflict regarding diabetes management and

decreased school performance. When interviewed alone, S.C. became tearful and reported that she is upset because "something is wrong with me." She denied any alcohol, nicotine, or recreational drug use. She denied current sexual activity, though she has been sexually active in the past.

Based on the information presented, major differential diagnoses under consideration are:

- Hypothyroidism
- Addison's disease
- Pregnancy
- Celiac disease
- Functional abdominal pain
- Irritable bowel syndrome
- Abdominal migraines
- Gastric ulcer
- MDD
- Anxiety disorder not otherwise specified
- Eating disorder not otherwise specified

At the conclusion of the clinic visit, additional lab work was ordered to support or refute the differential diagnoses. Lab results obtained indicated normal thyroid functioning (0.98 $\mu\text{U/ml}$; normal range 0.34–4.82), negative adrenal antibodies (normal), first-morning cortisol of 18 $\mu\text{g/dl}$ (normal range 5–25), negative serum human chorionic gonadotropin (HCG; normal), and serum tissue transglutaminase (tTG) of 100 U/ml (normal range < 4.0 U/ml).

A follow-up laboratory evaluation revealed that S.C. is positive for the celiac-specific autoantibody endomysial IgA. A subsequent endoscopy performed by a pediatric gastroenterologist ruled out an ulcer and provided evidence for celiac disease based on pathological report. S.C. was referred to a nutritionist for education and consultation and to begin a gluten-free diet. The family was also referred to the psychosocial team for additional assessment and support related to changes in diet and routine after diagnosis of celiac disease and to address normative anxiety symptoms related to current stressors.

S.C. initially did not want supportive psychotherapy; however, after attempting a gluten-free diet and having difficulty modifying her food choices with peers, she requested a consultation with the psychosocial team. She met four times with the diabetes team psychologist, who provided brief behavioral therapy focused on

adjustment to the celiac disease diagnosis and development of specific coping strategies.

Discussion

Signs and symptoms: depression versus medical illness

When dealing with children and adolescents with possible symptoms of depression in a typical diabetes outpatient visit, clinicians must be able to assemble all variables, including stability of medical condition (diabetes), associated diseases, and psychosocial functioning, into a unified picture. Because of the potential similarities among symptoms associated with depression and diabetes and the subsequent impact of depression on diabetes self-care, diabetes clinicians are in a unique position to identify physiological and psychological symptoms that may indicate increased risk for depression. These symptoms may include changes in appetite, weight gain or loss, abdominal pain, headache, decreased or increased exercise, school absences, and changes in involvement in peer or school activities.²⁶ Because there is an overlap in the symptoms and signs of depression and those of other medical conditions, it is essential to develop a thorough list of potential differential diagnoses and to rule out medical conditions before making the diagnosis of depression.

Identification of possible differential diagnoses are guided, in part, by type of diabetes, because different associated diseases occur more frequently in either patients with type 1 or type 2 diabetes. Autoimmune diseases are closely linked with type 1 diabetes because of their proximity on chromosome 6 in the HLA locus. Therefore, it is essential to consider conditions such as Hashimoto's thyroiditis, Graves' disease, celiac disease, and Addison's disease that pose an increased risk in children and teens with autoimmune type 1 diabetes.²³ Other conditions that may also be associated with type 1 diabetes and should be assessed in affected adolescents include postural orthostatic tachycardia syndrome (cardiogenic/neurogenic syncope),²⁷ subtle autonomic dysfunction,²⁸ and vitamin D deficiency.²⁵

Diseases associated with type 2 diabetes in children and adolescents include polycystic ovarian syndrome,²⁹ sleep apnea,²⁴ hyperlipidemia,³⁰ non-

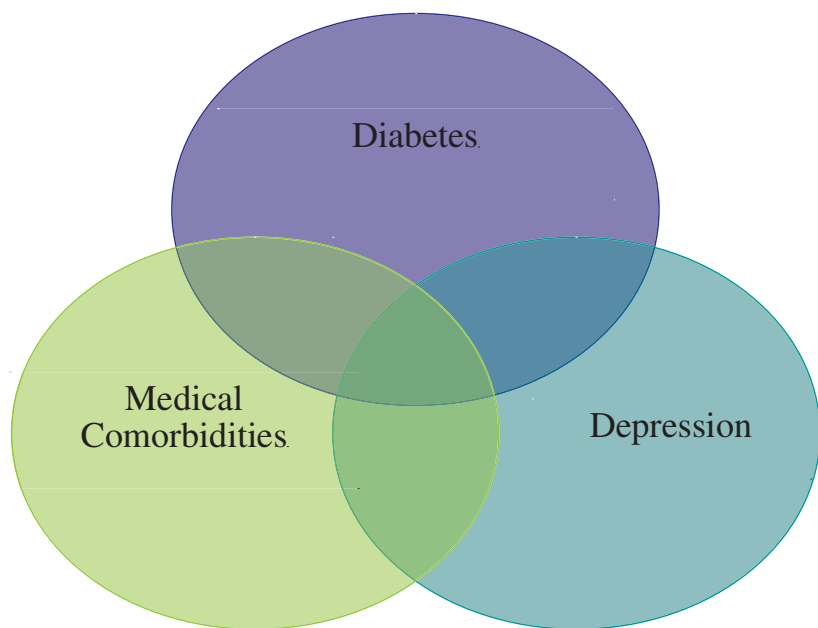


Figure 1. Overlap in symptoms of diabetes, medical comorbidities, and depression.

alcoholic steatohepatitis,³¹ metabolic syndrome,³² and asthma.³³ Additional conditions associated with the general adolescent population must also be considered, including pregnancy,³⁴ alcohol or recreational drug use,³⁵ and peer victimization.³⁶ Symptoms of many of these illnesses may, indeed, lead one to suspect depression, and, although depression may co-occur with the listed comorbidities, it is the responsibility of the diabetes clinician to perform thorough screening before reaching any conclusions about the etiology of the patient's symptoms.

In the case studies presented above, it was essential to rule out medically related conditions by additional directed questions, laboratory testing, and specialist referrals as needed. After results are evaluated, clinicians may be surprised to learn that what was believed to be depression was actually another medical condition causing similar symptomatology. Alternatively, after performing a laboratory work-up without yielding an alternate diagnosis, simple psychosocial screening tools may be employed in the office setting to confirm suspected depression. Lastly, it is also important to realize that comorbid medical conditions may actually contribute to increased symptoms of depression, because the related changes in lifestyle (e.g., changes in diet after a diagnosis of celiac dis-

ease) and an adolescent's perceived burden of symptoms may cause mood changes.

Screening during clinic visits

Pediatricians are starting to incorporate brief screening measures for depression as a part of routine care for children and adolescents. The recent Guidelines for the Management of Adolescent Development in Primary Care^{37,38} may be useful for clinicians in their efforts to screen for depressive symptoms during a typical clinic visit.

Many practitioners worry that screening for depression in primary care is too time-consuming and costly.³⁹ However, well-validated measures such as the Children's Depression Inventory⁴⁰ and the Center for Epidemiological Studies Depression Scale (CES-D)^{41,42} are self-report measures that are brief (30 items or fewer) and have empirically supported cut-off scores to identify children and adolescents at risk for depression. Additionally, the CES-D is free, eliminating the concern about cost of use.

Thus, incorporation of a screening measure or availability of a psychosocial screener to administer to select patients who appear to be at risk based on interview data is an important adjunct to medical treatment. The current American Diabetes Association (ADA) guidelines for care of children

and adolescents with type 1 diabetes⁴³ recommend an annual depression screening for children ≥ 10 years of age as part of routine best practices. Provision of appropriate referrals for children and adolescents if depression is suspected is a necessary part of routine care. If a diabetes team does not have psychosocial providers available for consultation and support, clinicians are encouraged to ask other team members or community members about possible psychosocial providers in their area with an expertise in behavioral health and chronic illness.

Team solution

It is imperative to conduct a thorough evaluation of possible differential diagnoses because of the overlap in symptomatology and to make referrals to appropriate specialists as needed. Assuming that a patient may have an underlying psychosocial issue may lead to missing a medical diagnosis by discounting significant symptoms and signs. Conversely, after discovering a medical diagnosis, clinicians should not assume that there is no need for supportive psychosocial therapy. The relationship among comorbid medical conditions and related stressors and lifestyle changes is complex, and adjustment difficulties may result in an increased risk for depression.

Rather than intervening after a problem is entrenched, use of a preventive intervention model advocates the identification and early intervention of patients at risk for a disorder. In the context of depression, early identification can alert a family to potential risk factors and hopefully prevent a depressive episode by enabling the patient and family to obtain support before the development of overt clinical symptoms.

Figure 1 graphically depicts the overlap among diabetes, medical comorbidities, and depression. In the shaded areas where two of the three circles overlap, screening is warranted to assess for possible depression or adjustment difficulties. In the center triangle where all three conditions overlap, referral to a mental health professional for in-depth evaluation is necessary.

To identify behavior change over time and uncover underlying emotions and sensitive issues, the development of a positive rapport between clinicians and their young patients is

Table 2. Tips for Diabetes Clinicians Working With Adolescents

- Identify and evaluate suspected differential diagnoses. Many symptoms of depression, including decreased energy, changes in sleep schedules, weight gain or loss, and memory difficulties, may also be indicative of other common comorbidities. Be thorough.
- Pay attention to the multiple spheres of adolescents' lives. Their daily lives consist of much more than diabetes management. Functioning in other areas can provide clues to support or rule out suspected differential diagnoses.
- Incorporate regular psychosocial screening measures to assess for depression. For adolescents who exceed the clinical cut-off score, have community referrals on hand to quickly provide the family with sufficient resources for further evaluation and treatment.

necessary. Patients must be viewed as whole people with multiple dimensions and not simply as children or adolescents with diabetes. Initiating sensitive conversations about social functioning (including discussions about sex, drugs, and alcohol) should be routine in each office visit, and it is strongly recommended that diabetes clinicians meet with teenage patients alone for a few minutes during each visit to answer any questions the adolescents may have, including questions related to alcohol and contraceptive use, which they may not want to discuss in the presence of parents. Gathering information about how well adolescents function in multiple spheres, including family, social groups, and school, contributes to making a skilled differential diagnosis and helps clinicians understand the bidirectional impact of diabetes and depression.

Given the increased risk of depression among teenagers with diabetes, the ADA recommends a brief psychosocial screening annually.⁴³ It is also important to screen for depression and provide appropriate follow-up when acute situations, including suicidal ideation or self-harming behaviors, emerge. Standardized questionnaires can be included in patients' ambulatory treatment records, along with annual laboratory evaluations. Questionnaires must be brief because of realistic time constraints of typical clinic visits. It is essential to act on the results gleaned from the questionnaires given to children and their caregivers. This requires scoring and recognition of clinical cutoffs at the time of the clinic visit with a clear follow-up plan, including discussion of significant results with the family, provision of appropriate referrals, and

an emergency plan to address acute suicidal ideation.

In addition to the use of screening tools, direct questioning about depressive symptoms and suicidal ideation is an effective technique to elicit information from adolescents and improve the quality of diagnostic data.³⁸ A behavioral contract between child and clinician during a clinic visit may be another method to help develop and sustain mutual goals between the child and the medical team, including follow-through with the recommended services. Table 2 offers tips for diabetes clinicians working with young patients.

Conclusion and Future Directions

Routine diabetes follow-up visits provide ample opportunity to screen and identify adolescents who may be at risk for depression. Although stress and some symptoms of depression, including increased fatigue and withdrawal from parents, may be somewhat normative during adolescence, the potential impact of depression on adherence and subsequent metabolic control is of particular concern and must be routinely addressed by pediatric clinicians. A thorough differential diagnosis, including medical and psychological conditions, is essential to identifying necessary interventions.

Although general depression screening tools exist, future efforts may be aided by the development of a diabetes-specific self-report questionnaire that can be easily administered in clinical settings to screen for depression and other psychosocial concerns. Depression may uniquely affect diabetes-related tasks, and diabetes-specific assessment may be important for early identification of depressive symptomatology.⁴⁴ Further development and evaluation of diabetes-specific therapy

techniques for adolescents dually diagnosed with diabetes and depression is another important area for future research.

Diabetes clinicians working with children and adolescents must be experts not only in diabetes management, but also in childhood and adolescent development, associated medical comorbidities, and psychosocial functioning. Diabetes clinicians are in a unique position to track behavior change and identify subtle clues that a child or adolescent may be at risk. Early identification and intervention may have profound impact on the lives of young patients. We need to make our limited time count.

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All of the authors are based in Washington, D.C. Maureen Monaghan, PhD, is a psychologist at Children's National Medical Center Department of Psychology, Childhood and Adolescent Diabetes Program. Chandra Singh, BS, is a medical student completing a research fellowship sponsored by the Society for Pediatric Research at the Children's National Medical Center. Randi Streisand, PhD, CDE, is the director of psychology research and services for the Childhood and Adolescent Diabetes Program at the Children's National Medical Center and an associate professor in psychiatry and pediatrics at George Washington University School of Medicine and Health Sciences. Fran R. Cogen, MD, CDE, is the director of the childhood and adolescent diabetes program in the Children's National Medical Center Department of Endocrinology and Diabetes and an associate professor of pediatrics at George Washington University School of Medicine and Health Sciences.