Psychiatric Manifestations in Individuals with Trisomy 21 (T21)

4. Depression in Trisomy 21 (T21)

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1. Overview

This module will address depressive disorder in individuals with Trisomy 21 (T21).
A separate condition, regression (with or without catatonia), is covered in Module 5: Regression and Catatonia.

According to the 2020 French National Protocol for Trisomy 21 (PNDS):

- **Depression is common in Trisomy 21 but is often under-recognized and undertreated.**
- Adolescents/adults with T21 and mild to moderate intellectual disability (ID) are at higher risk for depression.

Various factors contribute to depression, including a combination of biological, genetic, developmental, stress-related, and personality factors:

- In individuals with ID: there is an association between a biological predisposition and adverse psychosocial experiences, such as social rejection, loss, and failure. Due to limited cognitive comprehension and poor problem-solving abilities, coupled with social and interpersonal adaptation difficulties, the negative impact of these situations can be worse.
- In individuals with T21: similar risk factors as in the normal population or in individuals with other causes of ID may be involved, but exposure and sensitivity to these factors may vary. Additionally, individuals with T21 might have specific risk factors for depression (*Thom et al., 2021*).

2. Risk Factors

2.1. Neuroanatomical Correlations

2.2. Neurotransmitters

2.3. Somatic Pathologies and Life Events

2. Risk Factors

2-1: Neuroanatomical Correlations

- A smaller total brain volume has been shown to indicate a higher risk of depression. In the general population, ventricular enlargement, cortical atrophy, and sulcal widening have been linked to depression.

- Studies have shown that the overall brain volumes of individuals with T21 are smaller than those of the general population. In individuals with T21, increased expression of gene proteins located on chromosome 21 may lead to a cascade of effects in fetal brain structure development, resulting in a smaller brain volume with disproportionately reduced cerebellar volumes (*Pinter, Eliez, Schmitt, Capone, & Reiss, 2001*).

- Regarding specific brain structures, smaller hippocampal volumes are linked to recurrent depression in people with normal intellectual function.

- Using high-resolution MRI, Aylward et al., 1999, examined hippocampus, amygdala, and total brain volumes in 25 adults with T21 and 25 age-, sex-, and race-matched non-cognitively impaired adults. The authors reported that hippocampal volumes were disproportionately small for brain size in individuals with T21.

2. Risk Factors

2-2: Neurotransmitters

- Neurotransmitters play a crucial role in brain development and mood regulation. Reduced serotonin, gamma-aminobutyric acid, taurine, and dopamine levels have been found in the fetal frontal cortex of individuals with T21 (*Whittle et al., 2007*).

- Moreover, reduced serotonin tissue concentration seems to persist into adulthood and may lead to increased vulnerability to symptoms of depression and anxiety in individuals with T21 *(Seidl et al., 1999*).

2. Risk Factors

2-3: Somatic Pathologies and Life Events

- Somatic Pathologies:
  - **Hypothyroidism**, more prevalent in individuals with T21, is a well-known risk factor for depression in the general population (*Joffe, 2006*).
  - **OSAS (Obstructive Sleep Apnea Syndrome): the importance of "psychiatric" forms of presentation of OSAS**, and in particular depression in neurotypical adolescents *(Chang et al., 2017*), has been reported in adolescents and young adults with T21 *(Capone et al., 2013*). A survey conducted on 28 adolescents and young adults with T21, diagnosed with major depression by a mental health clinic for individuals with T21, showed that 86% of them had OSAS diagnosed by PSG, compared to 44% of non-depressed controls. Moderate to severe OSAS was evident in 54% of cases and 11% of controls (*Capone, 2013*).

  These OSAS/depression correlations are extensively discussed in the "Obstructive Sleep Apnea Syndrome (OSAS)" module in the "Respiratory Disorders" chapter.

- Life Events:
  - In their study on individuals with T21, Byrne & Seyfort, 1998, found that life events related to mourning and loss were present in 64.5%. They also documented evidence of physical and/or sexual abuse in 41% of participants.
  - Due to their life circumstances, individuals with T21 experience higher levels of loneliness, social isolation, self-hatred, and social withdrawal. These factors likely contribute to an increased risk of depression (*Ailey et al., 2006*).

3. Prevalence

- **Recent literature shows that depression prevalence in individuals with T21 ranges from 6% to 18%, with a higher prevalence in adults than in children, compared to the general population:**
  - Rivelli et al., 2022 (USA), in a retrospective population study of 6,078 individuals with T21 and 30,326 age- and sex-matched neurotypical controls, reported a depression prevalence of 9.4% vs. 7.6% in the general population (OR: 1.27 [1.15, 1.39]; P<0.0001).
  - Startin et al., 2020 (UK), demonstrated in 605 individuals with T21 (from 3 months to over 36 years old) a depression prevalence of 0% between 5.5 and 15 years / 12.4% between 16 and 35 years / 18.4% for adults over 36 years old. Furthermore, this prevalence is four times higher in females and five times higher in males compared to the general population.
- Dykens et al., 2015, in a study on 119 adolescents and young adults aged 13 to 29, found no difference in depression prevalence between individuals with T21 and people with ID of other origin.

4. Diagnosis

4.1. Considerations in Individuals with Intellectual Disability (ID)

4.2. Diagnostic Criteria according to DSM-5 and DM-ID2

4. Diagnosis

4.1. Considerations in Individuals with Intellectual Disability (ID)

There is a consensus that psychiatric disorders in individuals with intellectual disability present differently compared to the general population.

- This has led to the development of specific criteria:
  - Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities / Mental Retardation (*DC-LD; Royal College of Psychiatrists, 2001; Smiley & Cooper, 2003*);
  - Diagnostic Manual-Intellectual Disability *(DM-ID; Fletcher et al., 2007, DM-ID2, 2016*).

- These criteria are primarily formulated based on observable behavioral characteristics. Affective and cognitive symptoms, including depressed mood, guilt, worthlessness, and thoughts of death, are rarely verbalized, especially in individuals with a more severe level of disability (*Smiley & Cooper, 2003*).

4. Diagnosis

4.1. Considerations in Individuals with ID (continued)

The DM-ID2 (*Fletcher et al., 2016*) highlights several aspects to consider when diagnosing depression in people with intellectual disabilities:

1.Depression is easier to identify in individuals with milder ID and harder to diagnose when the person has more significant cognitive impairment and communication problems;

2. Communication difficulties and the heavy reliance on reports from caregivers make diagnosing potential depression more challenging in our work with individuals with ID because mood disorder diagnosis requires reliable information on internal states.

3. Developmental considerations impact the phenomenology of depression in people with ID, who exhibit characteristics similar to their mental age rather than their chronological age peers. This includes frequent findings of irritable mood, motor agitation, and the co-occurrence of behavioral disorders.

4. Diagnosis

4.1. Considerations in Individuals with ID (continued)

4. Although depressed individuals with ID show high rates of aggressive behavior and other externalizing behavior problems, these should not be used as "behavioral equivalents."

It is important to note that depression might go unnoticed if too much attention is paid to aggression issues, without conducting a broader examination of the person's mental state, mood, and biological functioning.

- Aggression may be best viewed as a "final common pathway" of distress in individuals with ID, who have few ways to express their distress;
- Aggression and other externalizing behaviors occur at high rates in association with most psychiatric disorders in individuals with ID and are not "diagnostically specific";
- Specific associations can be found, such as when a person with ID is depressed and behaves aggressively to avoid activities that might otherwise be enjoyable.

4. Diagnosis

4.1. Considerations in Individuals with ID (continued)

5. The differential diagnosis of depression in individuals with ID is complex as it requires considering how medical problems and medication side effects can influence clinical presentations.

- Classic symptoms of depression can be triggered by illness or medication side effects, so a person who appears anhedonic, irritable, withdrawn, and slowed down may be suffering from conditions such as constipation, drug-induced parkinsonism, dental problems, or acid reflux. Medical problems occur at higher rates in individuals with ID.

6. Individuals with ID may have complex presentations and meet criteria for multiple disorders, as observed in studies of the general population to date.

- High rates of comorbidity between depression and anxiety have been reported in patients with ID;
- Moreover, children and adults with ID might meet criteria defined for the new category of severe mood dysregulation (SMD). The implications of this disorder are not yet clear. Future studies could examine its usefulness in the population and identify individuals with ID who have developmental profiles similar to those in the target age group.

7. Although extensively studied, the biological basis of depression has not yet been fully elucidated. Long-standing models identifying genetic and psychosocial risk factors remain relevant but not explanatory.

4.2. Diagnostic Criteria

according to DSM-5 and DM-ID2

Diagnostic criteria according to DSM-5	Diagnostic criteria according to DM-ID2 for moderate to severe ID
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either: (1) Depressed mood (2) Loss of interest or pleasure. **Note**: Do not include symptoms that are obviously attributable to another medical condition.	Four (or more) symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either: (1) Depressed mood (2) Loss of interest or pleasure (3) Irritable mood **Note**: Do not include symptoms that are obviously attributable to another medical condition.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).	1. Depressed or irritable mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In people with ID, depressed mood may be described by others in one or more of the following ways, that constitutes a change from what is usually observed in this individual: sad facial expression, flat affect or absence of emotional expression, rarely smiles or laughs, cries or appears tearful. **Note:** Observers may describe individuals with ID who are irritable as: appearing grouchy or having an angry facial expression, having the onset of (or increase in) agitated behaviors (assaults, self-injurious behavior, spitting, yelling, swearing, disruptive or destructive behaviors) accompanied by angry affect.

4.2. Diagnostic Criteria

according to DSM-5 and DM-ID2 (continued)

Diagnostic criteria according to DSM-5	Diagnostic criteria according to DM-ID2 for moderate to severe ID
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.	2. No adaptation. **Note:** Observers may describe individuals with ID: refuses preferred activities, appears withdrawn, spends excessive time alone (more time than before), participates but shows no signs of enjoyment, becomes aggressive when asked to engage in activities previously enjoyed, has lost response to reinforcers, finds previously motivating events or objects no longer motivating, avoids social activities, becomes aggressive or agitated when prompted to attend social activities previously enjoyed.
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day.	3. No adaptation. **Note**: Observers may report that the person with ID: overeats, is preoccupied with food, steals food, refuses meals, has recently lost or gained weight, exhibits agitated behaviors during meals or regarding food (throws food on the floor, screams when the meal arrives).
4. Insomnia or hypersomnia nearly every day.	4. No adaptation. **Note:** Observers may report that the person with ID: has difficulty falling asleep, wakes up early in the morning, sleeps excessively, has shown a recent increase in problem behaviors late at night, very early in the morning, takes frequent naps, falls asleep during the day, is up and down all night, sleeps very little at night and seems tired.

4.2. Diagnostic Criteria

according to DSM-5 and DM-ID2 (continued)

Diagnostic criteria according to DSM-5	Diagnostic criteria according to DM-ID2 for moderate to severe ID
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).	5. No adaptation. **Note**: Observers may report that the person with ID: rarely sits down, is up and down from a seat a lot, paces, walks rapidly, fidgets, has slowed movements, has decreased or stopped talking, vocalizes much more or less than usual, is much less physically active than before.
6. Fatigue or loss of energy nearly every day.	6. No adaptation. **Note**: Observers may report the individual with ID: appears tired or reports feeling tired, refuses or becomes agitated about activities that require physical effort, spends excessive amounts of time just sitting or excessive amounts of time lying down, has dark circles under eyes.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).	7. No adaptation. Note: : Observers may report the individual with ID: makes negative self- statements; identifies self as a “bad” person; often expects punishment, without a history of harsh treatment; blames self for problems inappropriately; unrealistically fears caretakers will be angry or rejecting, even after minor transgressions; excessively seeks reassurances that he or she is accepted as a good person, or makes other negative self-statements at a high frequency (and this is a change from baseline). Note: People with Severe/Profound ID do not function at cognitive levels consistent with the capacity to experience or express feelings of guilt or worthlessness.

4.2. Diagnostic Criteria

according to DSM-5 and DM-ID2 (continued)

Diagnostic criteria according to DSM-5	Diagnostic criteria according to DM-ID2 for moderate to severe ID
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).	8. No adaptation. **Note:** Observers may report the individual with ID: shows a reduced productivity at work or day program, has diminished self-care skills, appears easily distracted or can't complete tasks he or she used to be able to finish, has shown the onset of or increase in agitated behaviors when asked to do activities that require concentration, has apparent memory problems that "come and go", has unexplained skill loss, shows an uncharacteristic inability to learn new skills as expected, or has had to stop working or attending programs due to poor performance.
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.	9. No adaptation. **Note:** Observers may report the individual with Mild/Moderate ID: often talks about death or people who have died or has other morbid preoccupations, has frequent unrealistic or unfounded physical complaints and fears of illness or death, makes threats to kill or harm self or has actually attempted suicide (unconventional means such as running in front of cars or jumping from windows may be impulsive acts, but may be suicidal in nature).

4.2. Diagnostic Criteria

according to DSM-5 and DM-ID2 (continued)

Diagnostic criteria according to DSM-5	Diagnostic criteria according to DM-ID2 for moderate to profound intellectual disability (ID)
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	No adaptation. **Note:** Individuals with ID may lose residential placements, jobs, vocational or other day programs due to apparent skill loss or associated disruptive behaviors, or there may be significant stress in the family or caretaking situation
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.	C. No adaptation. **Note:** Observers may report that for people with ID, almost any physical problem that causes pain or distress may also cause difficulty focusing attention, sleeping, eating and psychomotor agitation. In addition to direct causes for mood problems (problems in thyroid functions), infections, common medical problems may provoke symptoms that look like depression. These medical problems include: UTIs, otitis media, cellulites, fungal infections of the skin., etc., constipation, GERD, migraine headaches, or a variety of medication induced movement disorders (akathisia, other EPS) or other drug side effects (lethargy, sedation, delirium).
D. The episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.	D. No adaptation.
E. There has never been a manic episode or a hypomanic episode.	E. No adaptation.

5. Progression

5.1. Overview

5.2. Suicide Attempts

5. Progression

5-1: Overview

- According to the retrospective study by Cooper & Collacott, 1994, the mean age of onset of depression in individuals with T21 is 29.5 years, with a range of 11 to 50 years. Among participants with depression, 34 out of 42 participants (81%) had experienced a single depressive episode, while 8 patients (19%) had recurrent episodes.
- After an average interval of seven years, participants who had suffered from depression showed significantly more adaptive behavior disorders than participants without a history of psychiatric disorders (*Collacott & Cooper, 1992*).
- Furthermore, individuals with early-onset depression exhibited lower levels of adaptation than those with a later onset. The authors suggest that depression may interfere with the subsequent development of adaptive behavior. The skills of younger participants were acquired more recently and may therefore be more vulnerable to the effects of depression (*Cooper & Collacott, 1993*).
- Depression represents one of the most common neuropsychiatric comorbidities of Alzheimer's Disease (AD), but the relationship is complex. It has been demonstrated that individuals with a history of depression in early or mid-life have an increased risk of developing AD later in life. Alternatively, late-life depression may represent an early manifestation, or prodrome, of AD, given the strong temporal association with later AD development.
- Ly et al., 2023, consider chronic inflammation as a key mechanism linking obesity, AD, and depression, encompassing systemic inflammation due to metabolic disturbances, immune dysregulation via the gut microbiome, and direct interactions with amyloid pathology and neuroinflammation.

5. Progression
5-2: Suicide Attempts

There are few reports of suicidality in individuals with T21.

- A low rate of successful suicide might be due to several factors associated with cognitive impairments, such as an inability to cognitively link feelings of depression with thoughts of ending one's life, poor planning ability, and a lack of opportunity due to supervision by family or staff.
- Although cognitive impairment and poor planning abilities might limit the success of suicide plans, many suicidal acts are impulsive and do not require significant planning (*Hurley, 1998*).
- The DM-ID2 stresses the importance of exploring self-injurious statements and behaviors while limiting access to lethal means such as firearms and medications.
- Healthcare professionals must regularly assess the risk of suicide and depression in young people with ID. However, standardized assessment of suicidal thoughts and behaviors is challenging due to the lack of appropriate assessment tools. When screening patients with ID, clinicians often find themselves at a loss on how to directly inquire about the patient's current suicidal thoughts, past suicidal behavior, existence of suicidal plans, and access to means. Currently, there are no suicide screening tools specifically developed for young people with intellectual disabilities (*Ludi et al., 2012*).

6. Treatment

6.1. Pharmacotherapy

6.1.1 Therapeutic Experience at the Jérôme Lejeune Institute

6.2. Electroconvulsive Therapy

6.3. Psychotherapy

6.1. Pharmacotherapy

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed first-line medications for depression in the general population.

- In the population with T21:
  - In a recent retrospective study published in 2021 on the treatment of depression by SSRIs in adults with T21, Thom et al. report **that the treatment is generally well-tolerated and safe, and it is associated with clinically significant improvement in depressive symptoms in most patients treated.** However, prospective randomized controlled trials are needed to provide conclusive evidence.
  - Patients with T21 generally respond to lower doses of SSRIs than typically used in the general population.
  - In cases of delusional thoughts or hallucinations, the use of low-dose antipsychotics is recommended.
  - The usual treatment duration is two to three years.

6.1. Pharmacotherapy

6.1.1 Therapeutic Experience at the Jérôme Lejeune Institute

Based on our clinical experience at the Jérôme Lejeune Institute in psychiatric consultations and the records of patients followed and treated over decades, we have adopted some specific approaches in treating individuals with T21 experiencing a depressive episode:

- For patients with a history of cardiovascular disease, perform an ECG on-site whenever possible before starting antidepressant treatment. First, to rule out cardiac arrhythmia and second, to have a baseline ECG if other therapies are added (especially if a neuroleptic is added when psychotic features or disorganization are severe and not relieved by the antidepressant alone).
- Especially at the beginning of SSRI treatment in patients who have not received antidepressant treatment in the past, prioritize oral solutions of antidepressants (Paroxetine 20 mg/10 ml oral suspension, Fluoxetine 20 mg/5ml oral suspension). These oral solutions allow for a very slow increase in dosage.

  This has several advantages:
  - Improve clinical tolerance;
  - Detect the very minimum effective dose;
  - Detect overexcitement caused by exceeding the appropriate dose for each patient.

    (We have several anecdotal cases where the patient showed initial signs of improvement at doses of 1-2 mg/day of SSRIs, but became overexcited, with behavioral disturbances and insomnia when 1 mg more/day of SSRIs was added. The patient returned to a state of equilibrium within 24-48 hours when the SSRIs were reduced to the previously well-tolerated dose.)

6.2. Electroconvulsive Therapy

The effectiveness of electroconvulsive therapy (ECT) for patients suffering from major depressive disorder who do not tolerate or do not respond to antidepressant medications is well-known. This therapeutic option should not be ignored for children, adolescents, and individuals with ID.

- There are several case reports in the literature of ECT treatment in individuals with T21 with treatment-resistant major depressive disorder (*Gensheimer et al., 2002, Anthonio et al., 2022*).

- Although no generalizations can be made based solely on case reports, if applicable, ECT should be considered as a treatment for this patient population.

6.3. Psychotherapy

Traditionally, individuals with ID have had limited access to psychotherapeutic interventions.

- Willner, 2005, concluded that different psychotherapeutic modalities, including psychodynamic therapy, cognitive behavioral therapy, and cognitive therapy, can be effective in this group. However, treatment must be tailored to the cognitive abilities of the patients.
  - The same author concluded that current behavioral methods have been effective in controlling problem behaviors but have limited value for individuals with emotional problems.
- For depression, Cognitive Behavioral Therapy (CBT) has been adapted to the capabilities of people with mild ID.
  - Lindsay, Howells & Pitcaithly, 1993, demonstrated the feasibility of CBT in people suffering from depression and mild ID.
  - McCabe, McGillivray, & Newton, 2006, more recently, demonstrated the effectiveness of a CBT program administered by staff in a larger community sample of individuals with mild ID and depressive symptoms.
- Some authors (*Shadan et al., 2021*) advocate for psychotherapeutic interventions that prioritize the behavioral aspect (referred to as behavioral activation). Behavioral activation focuses less on verbal exchanges and more on increasing pleasant/meaningful activities for the patient and reducing avoidance behaviors.
- It is not known to what extent these results can be extrapolated to individuals with moderate to severe ID, including individuals with T21.

7. Key Points for Clinical Practice

- Depression is common in Trisomy 21 but is often under-recognized and undertreated.
- The prevalence of depression in individuals with T21 ranges from 6 to 18%, is higher in adults than in children, and is higher than in the general population.
- Individuals with T21 have specific vulnerability factors for developing depression: smaller hippocampal volumes, changes in neurotransmitter systems, high frequency of hypothyroidism, obstructive sleep apnea syndrome, as well as adverse psychosocial experiences, such as social rejection, loss, and failure.
- Though rare, the risk of suicide should be considered in individuals with T21.
- The diagnosis of depression mainly relies on observable behavioral symptoms and a precise medical history. The use of criteria adapted for individuals with ID, such as the DC-LD and DM-ID2 criteria, is recommended.
- Selective serotonin reuptake inhibitors are effective and well-tolerated in individuals with T21.
- There are also positive reports of electroconvulsive therapy in treatment-resistant depression among individuals with T21.
- Systematic evaluations of psychotherapeutic approaches for depression in individuals with T21 have not been reported to date. Cognitive behavioral therapy, tailored to the individual's cognitive abilities, may be an effective treatment option for individuals with T21 with mild ID.