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CREATE CHANGE

Down Syndrome Regression Disorder (DSRD)
What it is, and what can be done about it

Dr Cathy Franklin
Psychiatrist
Director, Mater Intellectual Disability and Autism Service (MIDAS)
Director, Qld Centre of Intellectual and Developmental Disability (QCIDD)

Acknowledgment of **Country**

The University of Queensland (UQ) acknowledges the Traditional Owners and their custodianship of the lands on which we meet.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

We recognise their valuable contributions to Australian and global society.

What is regression?

What is regression?

regression

- means going backwards in skills. It has a variety of causes.
- is the opposite of progression, which is a step forward – regression is a step back.
- is not uncommon. At various stages, children might regress, before progressing (may last a few weeks).
- occurs in autism in early childhood, where the child develops normally but then starts to lose speech and social skills. This can be slow or rapid and is often followed by a lengthy period of stagnant skill progression.
- can be caused by stress, physical illness, grief
- can occur in Autism Spectrum Disorder, Rett Syndrome, Landau- Kleffner syndrome, Alzheimer's disease, **Down syndrome (DSRD)**

Common conditions that can look like regression

Common conditions associated with regression in Down syndrome

- Thyroid disease
- Celiac disease
- Sleep apnea
- Hearing and eye conditions
- Constipation
- Dental problems
- Psychiatric problems – depression, anxiety, psychosis

- CHAP Online: https://www.health.gov.au/resources/publications/adult-comprehensive-health-assessment-program-chap-annual-health-assessment-for-people-with-intellectual-disability?language=en

- DSC2U: https://www.dsc2u.org/

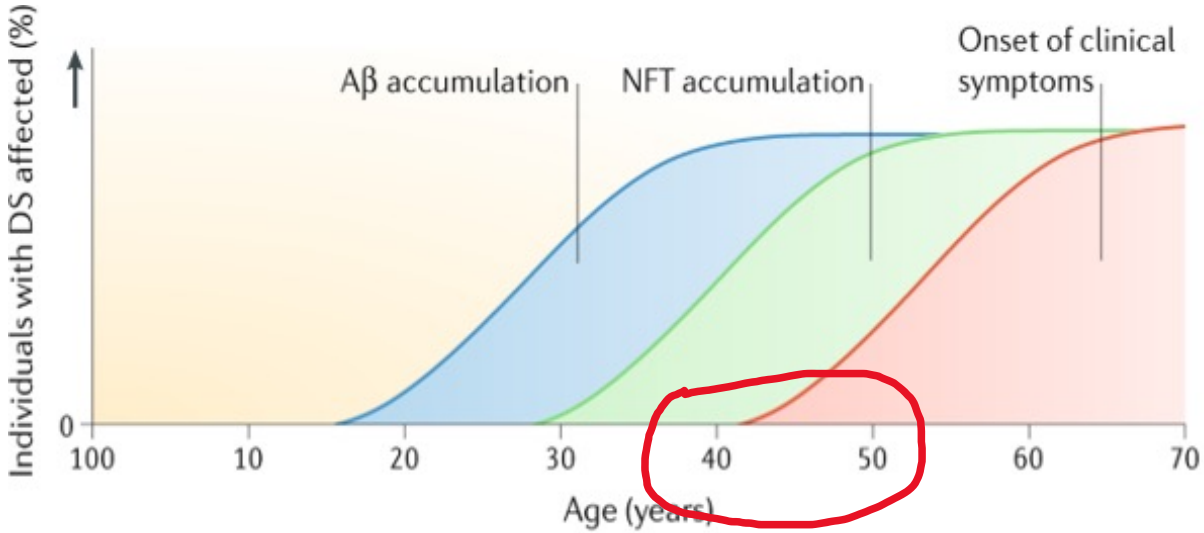
DSC2U
Down Syndrome Clinic to You

Uncommon conditions (see neurologist)

- Autoimmune encephalitis
- Stroke
- Epilepsy
- Heavy metal toxicity
- Additional genetic disorder associated with regression
- Mitochondrial disorders
- Infection (Lyme, HIV, Syphilis)
- Vitamin deficiencies
- Liver disease
- Electrolyte imbalance

- Mitochondrial disorders
- Organic acidurias
- Fatty acid oxidation disorders
- Urea cycle disorders
- Porphyria
- CDG
- Peroxisome storage disorders
- Lysosomal storage disorders

Common conditions…is it…dementia?



…dementia in Down syndrome is rare under 40. In clinic, even when we see patients over this age with problems, there is usually always something that is treatable, e.g. depression or constipation, that will improve someone's functioning and quality of life.

Is it…'late-onset autism'?

- Several features of DSRD are "autistic-like"
- **Autism diagnosis requires that features are present in the early developmental period.**
- Autism does not "come on" acutely in adolescence or adulthood.
- The assessing doctor needs to take a good developmental history and understand the premorbid functioning of the individual.

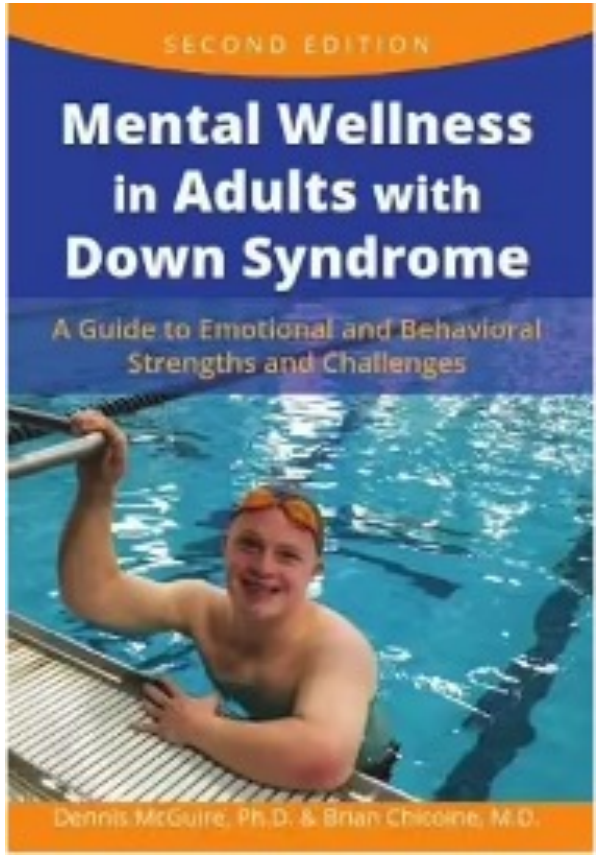
Caution!

1. People with DS-ASD can also develop DSRD. In this situation, there will be evidence of ASD early in their history well prior to regression.
2. Children with regression: More complex to tease out (ASD vs DSRD) and likely requires expert diagnostic assistance and testing.

Is it…'just Down syndrome' ?

- Concrete thinking
- Taking time (going slower)
- Language strengths and weaknesses
- Self-talk
- Getting (cognitively) stuck
- Memory (strong Visual / Visuo-spatial Memory)

Main areas of overlap are in a stress response, where we may see an increase in some of these features… (and DSRD is often associated with stressors)



Is it depression or psychosis?

DEPRESSION – Mood changes	PSYCHOSIS – Hallucinations, Delusions
Sad or irritable mood	Hallucinations*
Anhedonia (loss of interest or pleasure in activities)	Delusions
Insomnia	Insomnia
Weight gain or loss	Weight loss
Worthlessness, guilty thoughts	Disorganized speech or thought
Agitation	Agitation
Can be complicated by psychosis or catatonia	Can be complicated by catatonia

What is DSRD?

Different names in the literature

- Unexplained Regression in Down Syndrome (URDS)
- Down Syndrome Disintegrative Disorder
- Down Syndrome Neuropsychiatric Disorder
- Catatonia in Down syndrome

Consensus = Down Syndrome Regression Disorder (DSRD)

DSRD Consensus Diagnostic Criteria

Assessment and Diagnosis of Down Syndrome Regression Disorder: International Expert Consensus

Jonathan D. Santoro[1,2], Lina Patel[3], Ryan Kammeyer[4], Robyn A. Filipink[5], Grace Y. Gombolay[6], Kathleen M. Cardinale[7], Diego Real de Asua[8], Shahid Zaman[9], Stephanie L. Santoro[10], Sammer M. Marzouk[10], Mellad Khoshnood[1], Benjamin N. Vogel[2], Runi Tanna[2], Dania Pagarkar[2], Sofia Dhanani[2], Maria del Carmen Ortega[11], Rebecca Partridge[12], Maria A. Stanley[13], Jessica S. Sanders[14], Alison Christy[15], Elise M. Sannar[3,16], Ruth Brown[17], Andrew A. McCormick[5], Heather Van Mater[18], Cathy Franklin[19], Gordon Worley[20], Eileen A. Quinn[21], George T. Capone[22,23], Brian Chicoine[24], Brian G. Skotko[10,25] and Michael S. Rafii[2,26]*

Category	Criteria	Possible DSRD	Probable DSRD
Symptom onset	Onset of new neurologic, psychiatric, or mixed symptoms over a period of <12 weeks in previously health individual with Down syndrome	Yes	Yes
Clinical evidence of neurologic dysfunction	1. Altered mental status or behavioral dysregulation - Anorexia/decreased oral intake or hyperphagia - Confusion/disorientation - Inappropriate laughter - Encephalopathy 2. Cognitive decline - Apathy - Abulia and/or avolition - Acute memory impairment (including new difficulty with recall) 3. Developmental regression with or without new autistic features - Social withdrawal - Loss of previously developmental acquired milestones - Inability to perform activities of daily living - Stereotypy - Rigidity around routine changes - Decreased eye contact 4. New focal neurologic deficits on examination and/or seizure 5. Insomnia or circadian rhythm disruption 6. Language deficits - Expressive and/or receptive aphasia - Global aphasia (mutism) - Whispered speech 7. Movement disorder (excluding tics)* - Catatonia - Bradykinesia - Freezing - Gait disturbance 8. Psychiatric symptoms - Anxiety - Delusions or hallucinations - Derealization/depersonalization - Obsessive compulsive tendencies - Aggression/agitation	>3 symptom clusters present	>6 symptom clusters present
Exclusion of other etiologies	Reasonable exclusion of alternative causes of regression including other systemic and central nervous system disorders. Other primary psychiatric disorders are also considered exclusionary	Yes	Yes

*Must be included as one of the symptom clusters for possible or probable diagnosis.

What is DSRD?

Diagnostic Features:

- **Rapid and significant decline** in functional skills over the course of 6 months
- Perceived **decline** in cognitive (thinking) skills
- Unexplained **decline** in behaviour and mood
- **Significant** loss of speech
- Age 10-30 years, post-puberty when it starts
- Often associated with catatonia, depression, psychosis

Additional Symptoms

- Decrease interest in social experiences
- Change in eating, drinking, sleep
- Odd movements
- Slowness
- Freezing in positions
- Difficulty initiating movement
- Loops of motor behaviours
- Change in mood
- New onset or increase in self-talk

“Catatonia is a disorder of movement and control. It can make it hard for your brain to tell your body what to do.”

- It can make your body very slow, or even completely stuck and unable to move at all. (***stupor***)
- Your body might get stuck in unusual positions *(**posturing** – self; **catalepsy** – by examiner)*
- Your body might move differently, or feel stiff *(**rigidity**, **waxy flexibility, gegenhalten**)*
- You might have trouble speaking or stop speaking altogether. *(**mutism**)*
- Your thoughts, speech and body might get stuck on the same thing. *(Thoughts and speech: **verbigeration** – stuck record**, perseveration** – returning to same topic) (Body: **ambitendency**)*
- Your body might make unusual movements that you can’t control. *(**Mannerisms, stereotypies, tics**)*
- You might smile (***grimacing***), laugh or cry for no reason.
- It might be hard to chew or swallow.
- It might be hard to do your usual activities, so you might need more help with things like showering, dressing, toileting and moving.

Interview Questions for Support Person

Does the person ever

- get stuck in one position – if so, how long for? *(posturing)*
- get stuck in the middle of a movement – (*ambitendency)*
- need help getting started with a movement e.g. feeding self with cutlery, taking a step.
- get stuck in “loops” of behaviour? *(perseveration)*
- Have trouble crossing thresholds e.g. through doorways or up/down stairs
- Repeat other’s speech or movements? *(echolalia / echopraxia)*

Have you noticed:

- decreased speech / communication *(mutism)*
- increased slowness – e.g. How long does it take to eat breakfast now (compared to previously)?; How long does it take to get dressed now (compared to previously)? *(bradykinesia)*
- unusual movements – eye rolling back, repetitive frequent movements *(stereotypy)* or odd ways of doing usual behaviours *(walking backwards,* stepping sideways) *(mannerisms)*
- unusual facial expressions e.g. grimacing *(grimacing)*
- abnormal staring *(staring)*
- changing handed-ness (e.g. was always left but now right handed)
- periods of rushing around, agitation without obvious trigger *(agitation)*

NB: Inappropriate laughing and crying can also occur and be mistaken for hallucinations

Diagnostic Aids

HOME VIDEOS!

– Video of eating, video of getting stuck, video of walking, video of getting in car, video of any unusual things…

- Video showing function (esp speech) before regression

Case: Before DSRD

DSRD

More than one condition?

DSRD + marked motor disturbance – think DSRD + catatonia (v. common)

DSRD + negative mood, thoughts – think DSRD + depression

DSRD + visual or auditory hallucinations – think DSRD + psychosis

No loss of skills, and / or no change in communication, and / or no social withdrawal (losing them to another world – unlikely to be DSRD.

DSRD – Evidence Base

What do we know?

What we know so far…

- What it looks like
- The name
- What investigations should be done
- Psychosocial stressors may be involved in triggering it
- We have case reports and series to suggest that the best treatments are lorazepam, ECT and IVIg (insufficient evidence to rank these).

We don't know

- What causes it
- Any biomarkers or investigations to help prove the diagnosis
- How IVIg and immune-based treatments work – does it mean it is an immune-based condition?

We really lack sufficiently robust evidence to unequivocally insist that any of these treatments should be given, apart from lorazepam and / or ECT for catatonia – these are well-recognised treatments for catatonia.

Approach to Investigations

Basic Principles

Identify treatment targets

DSRD is a diagnosis of **exclusion:**

"Is this presentation better explained by…?"

1. **Medical or physical causes**
2. **Environmental causes** (psychosocial stressors, bullying, trauma, grief/loss, abuse)
3. **Psychiatric causes**

- catatonia
- depression
- psychosis

…but any of these can co-exist with DSRD

Consensus recommendations for investigations

Brain imaging: MRI with and without contrast on a 3T scanner

EEG

Blood tests

- FBE, E/LFT, ESR, CRP, Ammonia, HBA1C, Lipids, B12, Vit D,
- TFTs, Thyroid antibodies
- Celiac serology
- Autoimmune encephalitis panel

Lumbar puncture

- Cell count with differential, total protein, glucose, M/C/S,
- IgG index, Oligoclonal bands, autoimmune encephalitis panel

Santoro JD, Patel L, Kammeyer R, et al. Assessment and Diagnosis of Down Syndrome Regression Disorder: International Expert Consensus. Front Neurol. 2022 Jul Ghaziudd15;13:940175. PMID: 35911905.
Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9335003/

Approach to Management of DSRD

- Early Phase
- Later Phase

Early Stage Management: Education & Support

The skills are not lost – they are just buried

- What is catatonia and how does it affect someone (ie its not behavioural, its mechanical)
- What is DSRD etc
- Hope for improvement
- Reduce demands
- Expect to require significant increased support needs for first 3-6 months at least – document for NDIS

Early Stage Management: Diagnose and Treat

Assess, investigate, treat and education & support to person and family

Assess and investigate *(don't wait!)*

- Confirm diagnosis (physical examination and investigations), identify any mental illness, catatonia
- Swallow assessment may be necessary (catatonia can affect chew and swallow)

Treat (medications) *(don't delay!)*

- Treat catatonia: medication called lorazepam to maximum tolerated dose required for best response
- Once catatonia treatment is at its best, consider whether there are any left-over symptoms of depression or psychosis
- Consider immune treatments - IVIg
- Consider ECT in severe cases that don't respond to other treatments.

Later Phase Management

Learning to use skills again

Once the acute symptoms are improved, a rehab approach is helpful:

- Regular speech therapy to improve communication
- Regular exercise (physio or exercise physiology or personal trainer with experience in disability support)
- 1:1 support is often required to start accessing community again

Support with increased disability (in Australia, NDIS) support requirements is almost always necessary.

Psychiatric Management

Treatment of Catatonia

- Medication called lorazepam is first-line
- Other medications including atypical antipsychotics can be helpful
- Some anti-dementia drugs have also been reported to have some success in DSRD

Lorazepam

- First-line treatment in catatonia: seems more effective than other benzodiazepines
- I start at 0.5mg bd for a few days, if tolerated (no sedation), increase to 1mg bd then tds then introduce larger doses
- Average dose in large studies = 5mg / day; range 2-20mg
- My clinical experience = most are on 3-6mg / day, a couple on 10-12mg / day
- Instant effect once you hit the right dose
- Tolerance has not been a problem in any of our patients with catatonia (n=20-25)
- Don’t stop suddenly (risk withdrawal) and Do store in a safe and secure place!
- Lorazepam is not on the PBS and as it is available as a generic, the parent company is not interested in pursuing PBS listing. It costs $0.8-1/1mg tablet on a private script. This makes it expensive for treatment of catatonia.
- IV lorazepam challenge is advocated by some centres but is difficult to access in our healthcare system (and not 100% helpful).

Anti-psychotics and anti-depressants

- Use half normal dose in people with Down syndrome to achieve same result
- Try to avoid any that cause weight gain

Antipsychotics

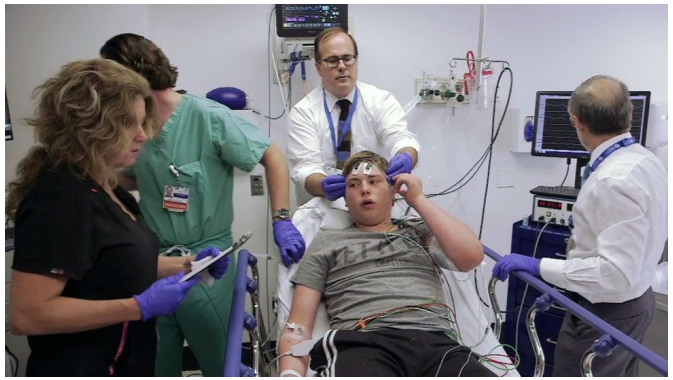
- My current first-line choice is lurasidone (less weight gain, less sedation) – I have seen 2 cases of aggressive food-seeking necessitating change to another medication
- Most don't tolerate aripiprazole or brexpiprazole although these have better side effect profiles for weight etc
- Risperidone can be effective
- Olanzapine is most effective but will cause significant weight gain so is reserved for desperate situations

Antidepressants

- Only useful where anxiety or depressive symptoms present
- I have had some patients develop anxiety symptoms (panic attacks) that we initially thought was catatonic excitement – responded well to SSRI treatment
- SSRI's are first line, have not found additional benefit with SNRI or Tricyclic antipdepressants

ECT

- ECT (electroconvulsive therapy) involves delivering an electrically induced seizure to an anaesthetised patient
- Brief general anaesthetic – patient is totally asleep and given muscle relaxant to prevent muscle contraction
- Seizure lasts up to 1 minute
- Patient is awake after a few minutes
- Affects memory at time of treatment
- Large-scale studies suggest no lasting memory impairment
- Reserved for cases where other treatments don’t work
- Effective treatment at getting someone well but not at preventing relapse
- Initial treatment 3 times / week for 4 weeks, then increasingly spaced out, may need fortnightly or monthly treatments for 1-2 years
- In Qld, classified as a special treatment: need to have second opinion and to apply for approval by MHRT (parent’s consent is not enough)



IVIg and Immune Treatments

- Dr Jon Santoro

How to find help??!!

General Tips

- If you think something is wrong, get it checked out
- Keep up with annual health and dental checks, vision and hearing
- Maximize strengths
- Be mindful of grief and loss, especially around time when school is finishing, siblings are moving out of home, transition to adult services
- If looking for help, look for someone who listens and is genuinely interested
- If someone needs medication, in DS, I recommend starting at half the standard starting dose or even a quarter, increasing slowly. Final doses usually only need to be half the standard dose.

Finding help?

- Best outcome is if you can find someone local who can see the person unwell and become an ally in their treatment.
- I advise you will need GP, psychiatrist and ideally neurologist – neurologist is harder to find (and psychiatrist can be hard enough!)

RESOURCES

General Resources

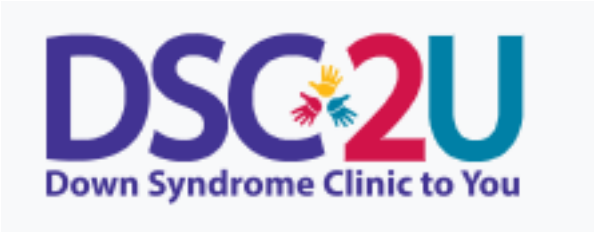
Health Check Tools

CHAP (Comprehensive Health Assessment Program) developed by Prof Lennox, QCIDD

- Now licensed and available due to Aust Govt investment, free to download
- Provides documentation to support an annual health check
- Was basis for Medicare to introduce special item number for annual health checks for people with intellectual disability
- Intellectual disability, not DS-focussed but does have DS-specific information
- https://chaphealth.com

DSC2U

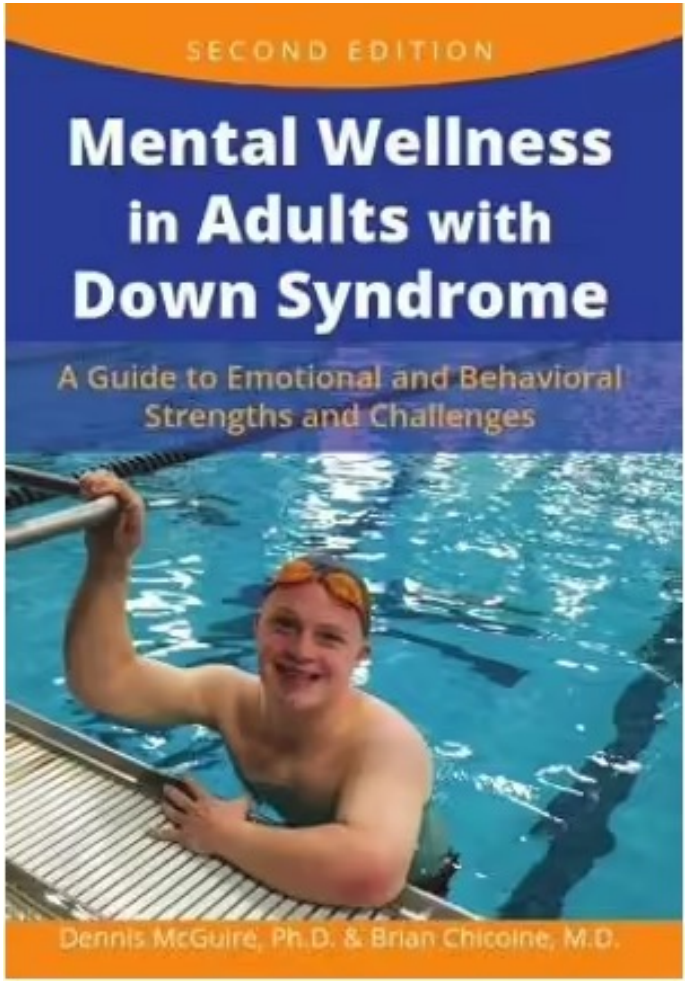
- Developed by Prof Brian Skotko and team, USA
- Online, DS-specific health assessment tool that screens for symptoms
- Fee-based (minimum $49USD per year)
- https://www.dsc2u.org



Dennis McGuire and Brian Chicoine's book "Mental Wellness in Adults with Down Syndrome", 2021

NOW available for download at:

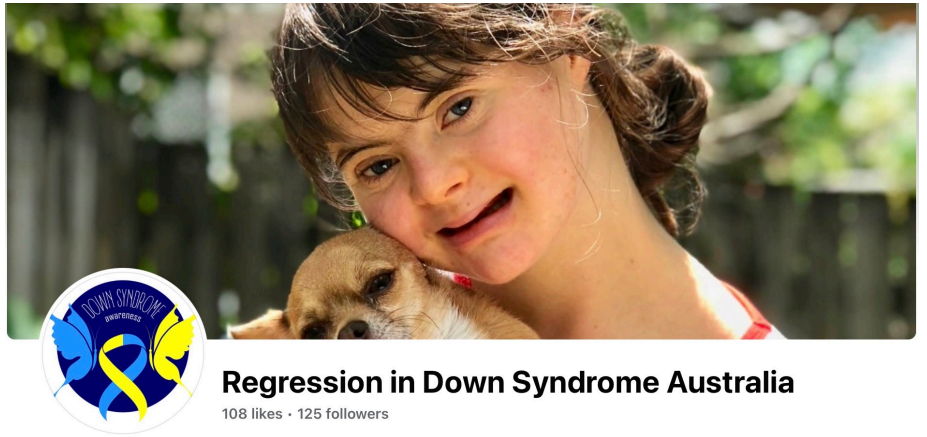
https://adscresources.advocatehealth.com/mental-wellness-in-adults-with-down-syndrome-2nd-edition/



Facebook Groups

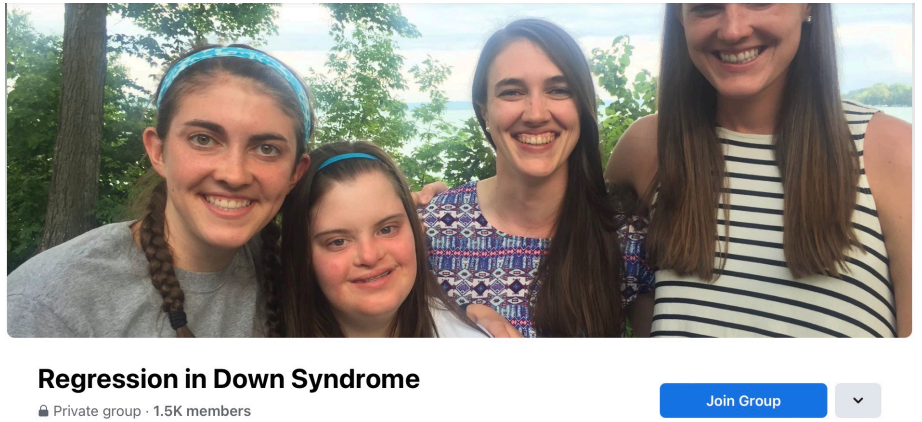
Australian Group (small)

https://www.facebook.com/DSRDAustralia/



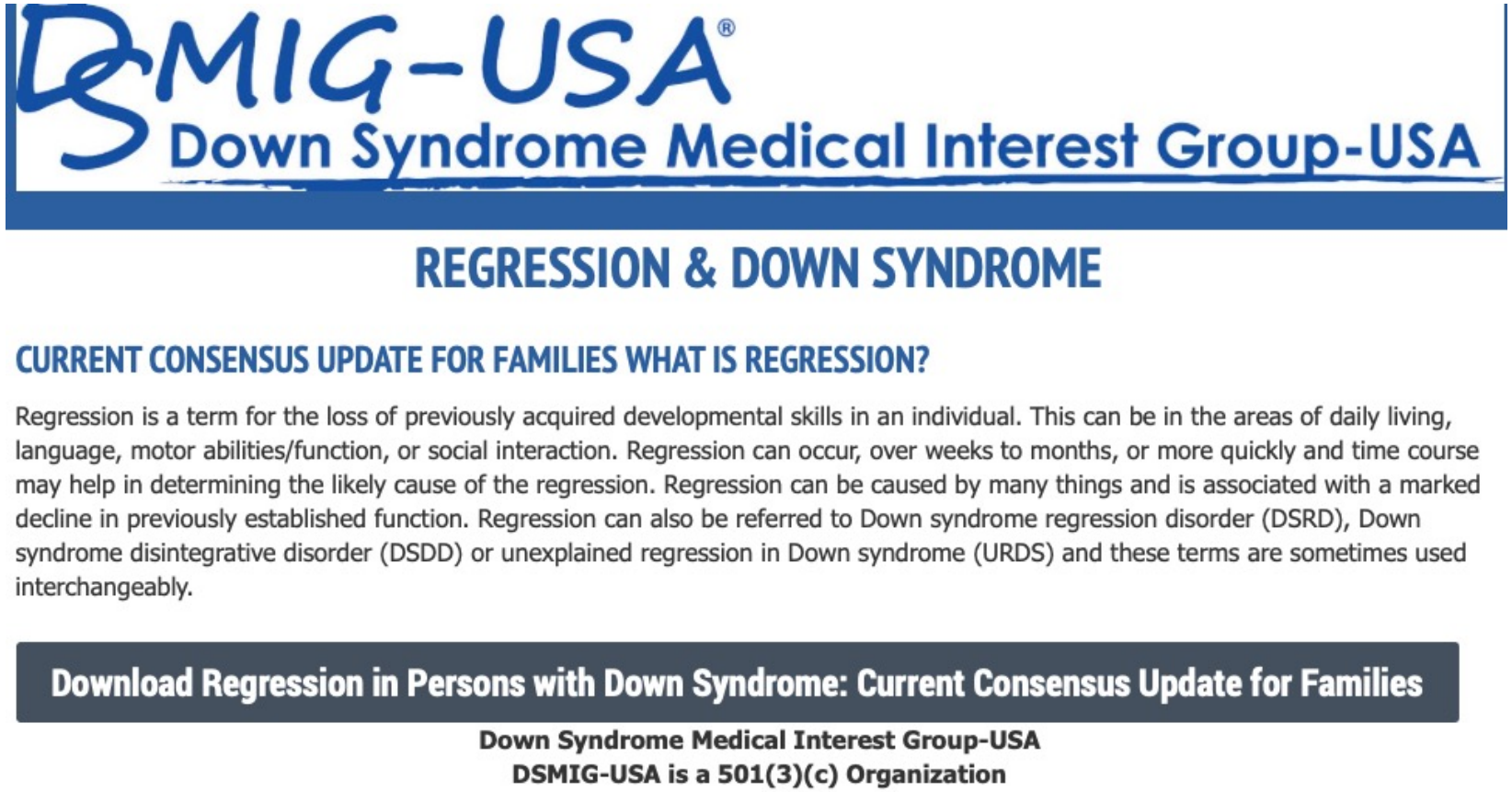
USA Group (large)

https://www.facebook.com/groups/regressionindownsyndrome/



Resources for Families

DSRD Information for Families


DSMIG-USA®
Down Syndrome Medical Interest Group-USA

REGRESSION & DOWN SYNDROME

CURRENT CONSENSUS UPDATE FOR FAMILIES WHAT IS REGRESSION?

Regression is a term for the loss of previously acquired developmental skills in an individual. This can be in the areas of daily living, language, motor abilities/function, or social interaction. Regression can occur, over weeks to months, or more quickly and time course may help in determining the likely cause of the regression. Regression can be caused by many things and is associated with a marked decline in previously established function. Regression can also be referred to Down syndrome regression disorder (DSRD), Down syndrome disintegrative disorder (DSDD) or unexplained regression in Down syndrome (URDS) and these terms are sometimes used interchangeably.

Download Regression in Persons with Down Syndrome: Current Consensus Update for Families

Down Syndrome Medical Interest Group-USA
DSMIG-USA is a 501(3)(c) Organization

https://www.dsmig-usa.org/Regression

Resources for Doctors

Webinar for Medical & Health Professionals

https://www.dsmig-usa.org/Speaker-Series

SESSION V & VI: REGRESSION & DOWN SYNDROME

Date: March 14, 2023 – Part 1 & May 9, 2023 – Part 2
Time: 7:00 – 8:00 PM EST

Individuals with Down syndrome may experience regression in previously acquired skills. This two-part webinar will present panel discussions on regression, with a key focus on Down Syndrome Regression Disorder (DSRD). This condition occurs most commonly between the ages of 10 and 30 years and is associated with loss of skills in language, cognition, behavior, motor and adaptive skills. Discussion will include what we currently know about DSRD diagnosis and management.

Part 1 Speakers	Part 2 Speakers
Eileen A. Quinn, MD UT College of Medicine and Life Sciences **Lina Patel, PsyD** University of Colorado School of Medicine **Robyn Filipink, MD** UPMC's Children's Hospital of Pittsburgh **Dr Cathy Franklin** QCIDD Queensland Centre for Intellectual and Developmental Disability Mater Research Institute - University of Queensland	**Eileen A. Quinn, MD** UT College of Medicine and Life Sciences **Lina Patel, PsyD** University of Colorado School of Medicine **Jonathan Santoro, MD** Assistant Professor of Neurology at CHLA and the Keck School of Medicine at USC **Cassie Karlsson, MD** Director - Child and Adolescent Psychiatry Fellowship Program & Clinical Associate Professor Department of Psychiatry and Behavioral Sciences at UK School of Medicine – Wichita

WATCH PART 1 RECORDING HERE

WATCH PART 2 RECORDING HERE

Medical papers

Overview

Rosso M, Fremion E, Santoro SL, et al. Down Syndrome Disintegrative Disorder: A Clinical Regression Syndrome of Increasing Importance. Pediatrics. 2020 Jun;145(6):e20192939. doi: 10.1542/peds.2019-2939. PMID: 32471843. • Freely available at: https://publications.aap.org/pediatrics/article/145/6/e20192939/76920/DownSyndrome-Disintegrative-Disorder-A-Clinical

Santoro SL, Cannon S, Capone G, et al. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. Genet Med. 2020 Apr;22(4):767-776. doi: 10.1038/s41436-019- 0706-8. Epub 2019 Nov 26. PMID: 31767984. • Freely available at: https://www.gimjournal.org/article/S1098-3600(21)01149-7/fulltext

Diagnosis and Assessment

Jacobs J, Schwartz A, McDougle CJ, Skotko BG. Rapid clinical deterioration in an individual with Down syndrome. Am J Med Genet Part A. 2016 Jul; 170A(7):1899-1902. PMID: 27149638. • Freely available at: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajmg.a.37674

Poumeaud F, Mircher C, Smith PJ, Faye PA, Sturtz FG. Deciphering the links between psychological stress, depression, and neurocognitive decline in patients with Down syndrome. Neurobiol Stress. 2021 Feb 5;14:100305. doi: 10.1016/j.ynstr.2021.100305. PMID: 33614867; PMCID: PMC7879042. • Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7879042/

Santoro JD, Patel L, Kammeyer R, et al. Assessment and Diagnosis of Down Syndrome Regression Disorder: International Expert Consensus. Front Neurol. 2022 Jul Ghaziudd15;13:940175. PMID: 35911905. • Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9335003/

Treatment

Ghaziuddin N, Nassiri A, Miles JH. Catatonia in Down syndrome; a treatable cause of regression. Neuropsychiatr Dis Treat. 2015 Apr 2;11:941-9. doi: 10.2147/NDT.S77307. PMID: 25897230; PMCID: PMC4396650. • Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4396650/

Miles JH, Takahashi N, Muckerman J, et al. Catatonia in Down syndrome: systematic approach to diagnosis, treatment and outcome assessment based on a case series of seven patients. Neuropsychiatr Dis Treat. 2019 Sep 20;15:2723-2741. doi: 10.2147/NDT.S210613. PMID: 31571888; PMCID: PMC6759875. • Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6759875/

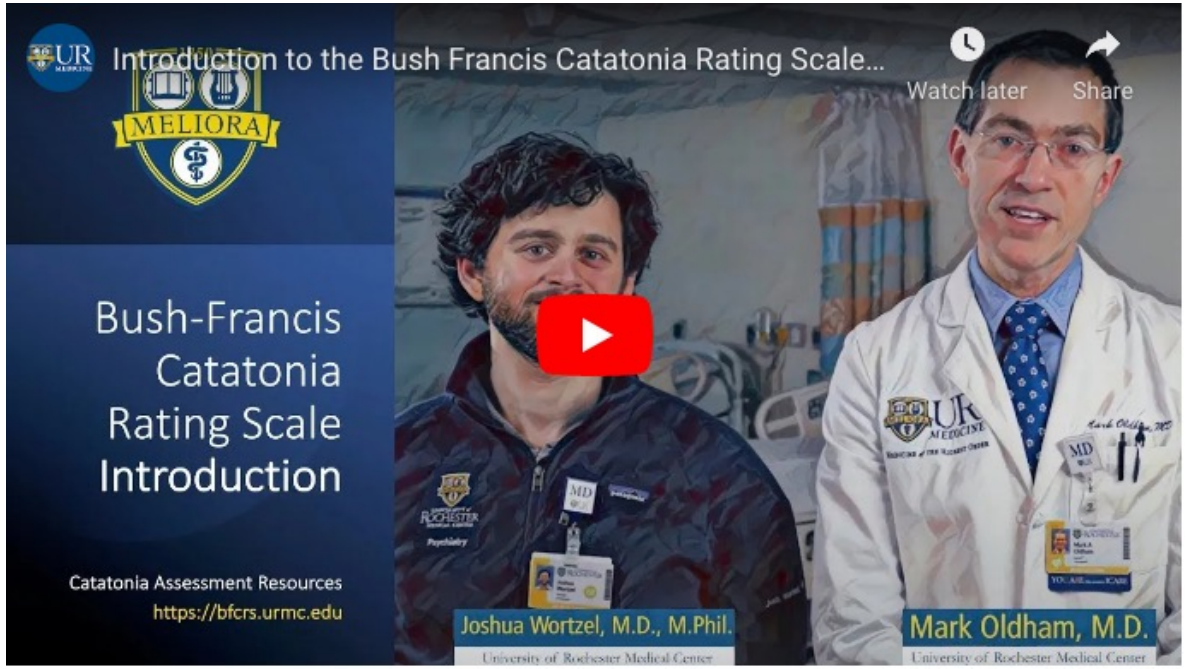
Santoro JD, Partridge R, Tanna R, et al. Evidence of Neuroinflammation and Immunotherapy Responsiveness in Individuals with Down Syndrome Regression Disorder. J Neurodev Disord. 2022 Updated January 2023 Jun 3;14(1):35. PMID: 35659536. • Freely available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9164321/

Santoro SL, Cannon S, Capone G, et al. Unexplained regression in Down syndrome: 35 cases from an international Down syndrome database. Genet Med. 2020 Apr;22(4):767-776. doi: 10.1038/s41436-019- 0706-8. Epub 2019 Nov 26. PMID: 31767984. • Freely available at: https://www.gimjournal.org/article/S1098-3600(21)01149-7/fulltext

Catatonia Examination and Bush-Francis Scale

Bush-Francis Catatonia Scale and Video Training (University of Rochester, USA)

https://www.urmc.rochester.edu/psychiatry/divisions/collaborative-care-and-wellness/bush-francis-catatonia-rating-scale.aspx



Questions?

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
CREATE CHANGE

Thank you

DrCathyFranklin
Dr Cathy Franklin
DrCathyFranklin
Cathy Franklin

Email: c.franklin1@uq.edu.au
midas@mater.org.au