Te Kāwanatanga o Aotearoa
New Zealand Government

MINISTRY OF HEALTH
MANATŪ HAUORA

Supplementary material:

Addendum to *Impact of Puberty Blockers in Gender-Dysphoric Adolescents: An evidence brief*

November 2024

Table 1: Studies on epidemiology and physical health included in the addendum

Study and country	Type of article	Study type	Study aim	Treatment	Comment	Quality[1]
Physical						
Boogers LS, Reijtenbagh SJP, Wiepjes CM, et al. 2023. Time course of body composition changes in transgender adolescents during puberty suppression and sex hormone treatment. *Journal of Clinical Endocrinology and Metabolism*. DOI: 10.1210/clinem/dgad750. Netherlands	Peer-reviewed original research American College of Obstetricians and Gynecologists study	Retrospective longitudinal observational	Body composition	Triptorelin 3.75 mg 1 × per 4 weeks, or 11.25 mg 1 × per 10 to 12 weeks	In both transgender boys and transgender girls, treatment with GnRHa resulted in a decrease in lean mass z-scores and an increase in fat mass z-scores.	Good
Fisher AD, Ristori J, Romani A, et al. 2023. Back to the future: is GnRHa treatment in transgender and gender diverse adolescents only an extended evaluation phase? *Journal of Clinical Endocrinology and Metabolism* 109(6): 1565–79. DOI: 10.1210/clinem/dgad729. Italy	Peer-reviewed original research	Prospective longitudinal observational	Relationship between psychological wellbeing and body composition	Triptorelin 3.75 mg every 28 days, interval adjustments based on clinical and laboratory data	Psychological improvement in transgender and gender diverse adolescents on GnRHa seems to be related to the objective body changes induced by a GnRHa.	Poor

[1] Newcastle Ottawa Scale.

Study and country	Type of article	Study type	Study aim	Treatment	Comment	Quality[1]
Perl L, Elkon-Tamir E, Segev-Becker A, et al. 2021. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *Journal of Pediatric Endocrinology and Metabolism* 34(6): 741–5. DOI: 10.1515/jpem-2021-0172. Israel	Peer-reviewed original research	Retrospective longitudinal observational	Cardiovascular	Decapeptyl 3.75 mg every 4 weeks	Based on the findings in this pilot study, the authors suggest that pubertal suppression with GnRHa may increase DBP in transgender male adolescents, but it does not cause hypertension.	Good
Roy MK, Bothwell S, Kelsey MM, et al. 2024. Bone density in transgender youth on gender-affirming hormone therapy. *Journal of the Endocrine Society* 8(5). DOI: 10.1210/jendso/bvae045. United States	Peer-reviewed original research	Cross-sectional (secondary analysis of data)	Bone health	GnRHa schedule not reported	Total body BMD z-scores ascertained by DXA were slightly below average for female and male norms, but still in the normal range, including for those who were on GnRHa monotherapy.	Poor
van der Loos MATC, Vlot MC, Klink DT, et al. 2023. Bone mineral density in transgender adolescents treated with puberty suppression and subsequent gender-affirming hormones. *JAMA Pediatrics* 177(12): 1332–41. DOI: 10.1001/jamapediatrics.2023.4588. Netherlands	Peer-reviewed original research	Prospective longitudinal observational	Bone health Primary aim to assess gender-affirming hormone treatment	Triptorelin 3.75 mg, every 4 weeks or 11.25 mg every 10 to 12 weeks	For individuals AMAB, the z-scores were already lower than 0 at the start of a GnRH agonist treatment and further decreased during that treatment. For AFAB individuals, the BMD z-scores decreased after the start of GnRH agonist treatment.	Good
Waldner R, Doulla M, Atallah J, et al. 2023. Leuprolide acetate and QTc interval in gender-diverse youth. *Transgender Health* 8(1): 84–8. DOI: 10.1089/trgh.2021.0102. Canada	Peer-reviewed original research	Retrospective cross-sectional observational research	Cardiac	Leuprolide. Dose not stated	No gender-diverse youth on leuprolide acetate demonstrated clinically significant prolonged QTc. Analysis by assigned or affirmed gender was not possible.	Poor

Study and country	Type of article	Study type	Study aim	Treatment	Comment	Quality[1]
Fertility						
No studies identified						
Epidemiology						**Quality[2]**
Gutiérrez K, Moreno M, Sierra JA, et al. 2024. Characteristics of the paediatric population with gender incongruence attending specialized care in Cali, Colombia: an observational, descriptive and retrospective study. *Child and Adolescent Psychiatry and Mental Health* 18(1): 1. DOI: 10.1186/s13034-023-00689-6. Colombia	Peer-reviewed original research	Observational retrospective	Age at development of gender dysphoria/incongruence	GnRHa schedule not described	The median age of onset of gender incongruence was 10 years (IQR: 5–13 years). The median time elapsed between the reported onset of gender incongruence and the first consultation with a multidisciplinary gender-affirming team was 3 years (IQR: 1–10 years).	93%

Table 2: Papers included after full review – impact of puberty blockers on mental health and wellbeing outcomes

Study	Outcomes	GRADE quality	Risk of bias
Fisher AD, Ristori J, Romani A, et al. 2023. Back to the future: is GnRHa treatment in transgender and gender diverse adolescents only an extended evaluation phase? *Journal of Clinical Endocrinology and Metabolism* 109(6): 1565–79. DOI: 10.1210/clinem/dgad729.	Gender dysphoria Anxiety Depression Quality of life Suicidality	Very low Very low Very low Very low Very low	Critical Critical Critical Critical Critical
McGregor K, McKenna JL, Williams CR, et al. 2024. Association of pubertal blockade at Tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. *Journal of Adolescent Health* 74(4): 801–7. DOI: 10.1016/j.jadohealth.2023.10.028.	Quality of life / social wellbeing Self-harm Suicidality	Low Very low Very low	Moderate Serious Serious

[2] Crowe Critical Appraisal Tool.

Study	Outcomes	GRADE quality	Risk of bias
McPherson S, Freedman DEP. 2024. Psychological outcomes of 12–15-year-olds with gender dysphoria receiving pubertal suppression in the UK: assessing reliable and clinically significant change. *Journal of Sex and Marital Therapy* 50(3): 315–25. DOI: 10.1080/0092623X.2023.2281986.	Quality of life / social wellbeing	Very low	Critical
van der Miesen AIR, Steensma TD, de Vries ALC, et al. 2020. Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers. *Journal of Adolescent Health* 66(6): 699–704. DOI: 10.1016/j.jadohealth.2019.12.018.	Suicidality	Very low	Serious

Table 3: Papers included after full review – targeted mental health and wellbeing interventions

Study	Intervention	Quality
Morgan H, van Hall HW, Moore JK, et al. 2024. A pilot group program for parents of trans young people at a specialized pediatric gender diversity service. *LGBTQ+ Family: An Interdisciplinary Journal*. DOI: 10.1080/27703371.2024.2347495.	Parent/carer targeted Psychologist-facilitated group designed for parental/carer understanding and acceptance of and support for their child	Low
Mackie G, Patlamazoglou L, Lambert K. 2023. The experiences of Australian transgender young people in school counseling: an interpretative phenomenological analysis. *Psychology of Sexual Orientation and Gender Diversity* 10(2): 337–49. DOI: 10.1037/sgd0000544.	Adolescent targeted School-based counselling at secondary school level	High

Active clinical trials on puberty blockade in gender-dysphoric adolescents

Table 6 describes active clinical trials on puberty blockade in gender-dysphoric adolescents, which were all identified through ClinicalTrials.gov. No additional trials relevant to GnRHa therapy for gender dysphoria were identified in the Australian New Zealand Clinical Trials Registry[3] or European Union Clinical Trials Register.[4] It is likely that other studies are under way across jurisdictions that may not have been registered on any of these sites.

Table 6: Active clinical trials on puberty blockade in gender-dysphoric adolescents

Trial name	Trial number	Status	Aim	Study type	Cohort	Location
Epidemiology						
Gender Dysphoria: Epidemiological Data (DyGenEpi)	ClinicalTrials.gov ID NCT04573127	Unknown	To conduct a retrospective study in a single academic regional transgender referral centre. Data from the cohort follow-up in CHRU de Nancy.	Observational	All individuals (any age) with a diagnosis of gender dysphoria attending a specialist gender clinic.	France
Cardiometabolic						
Puberty Blockade and Hormone Therapy in Transgender Youth (PUBErTY)	ClinicalTrials.gov ID NCT04596592	Completed; no results reported	To study the effects of pubertal blockade and hormone therapy on cardiometabolic risk markers in transgender adolescents.	Prospective observational	Transgender males (AFAB), who: • are aged 13–16 years at the time of enrolment • if on a GnRHa, have had more than six months exposure • plan to start testosterone clinically in less than six months.	United States
The Relation of GnRH Treatment to QTc Interval in Transgender Females	ClinicalTrials.gov ID NCT03078829	Terminated: No results posted	To assess the effect of GnRH agonist treatment on QTc interval in transfemale youth.	Prospective observational	Transgender females 10 years or older: • child • adult • older adult	United States

[3] URL: **anzctr.org.au/** (accessed 12 June 2024).

[4] URL: **clinicaltrialsregister.eu/ctr-search/search** (accessed 12 June 2024).

Trial name	Trial number	Status	Aim	Study type	Cohort	Location
Pubertal Blockade and Estradiol Effects on Cardiometabolic Health for Transitioning Youth (PUBERTY)	ClinicalTrials.gov ID NCT04596592	Recruiting	To evaluate the effect of estradiol with or without a prior GnRHa on insulin sensitivity and vascular function in transgender females compared with cisgender controls.	Prospective observational	People who identify as a transgender female who: • were aged 13–16 years at the time of enrolment • if on a GnRHa, have had more than six months exposure • plan to start estradiol clinically in less than four months.	United States
Bone health						
Skeletal Health and Bone Marrow Composition among Youth		Active	To identify the effects of pubertal blockade on bone density and size in paediatric transgender individuals.	Interventional (non-randomised)	Individuals aged 9–14 years identifying as transgender or binary.	United States
Skeletal Health and Bone Marrow Composition among Youth	ClinicalTrials.gov ID NCT04203381	Recruiting	To examine bone marrow composition (by MRI) in 40 transgender youth and bone density and body composition before and after pubertal blockade, compared with healthy participants.	Observational longitudinal study Multi-centre	Children aged 9–14 years with a diagnosis of gender dysphoria cared for at a specialist gender clinic.	United States
Fertility						
Ovarian Tissue Cryopreservation in the Setting of Gender-affirming Therapy	ClinicalTrials.gov ID NCT05863676	Recruiting	• To optimise techniques for cryopreservation of ovarian tissues, including determining efficacy of cryopreservation techniques. • To investigate factors affecting ovarian tissue and follicles, such as previous treatment with leuprolide acetate, or hormone therapy.	Prospective observational	• Transmales (AFAB) aged nine years or older with a diagnosis of gender dysphoria. • Patients aged nine years or older who are on or about to start puberty blockers or hormone treatment. • Patients over the age of 18 years about to undergo oophorectomy.	United States
Testicular Tissue Cryopreservation in the Setting of	ClinicalTrials.gov ID NCT05829928	Recruiting	• To optimise techniques for processing and cryopreserving testicular tissue.	Longitudinal observational	• Transfemales (AMAB) aged nine years or older with a diagnosis of gender dysphoria.	United States

Trial name	Trial number	Status	Aim	Study type	Cohort	Location
Gender-affirming Therapy			• To determine the presence and number of germ cells (sperm precursors) in the patients' testicular tissue. • To develop next-generation cell- and tissue-based therapies for preserving fertility and treating infertility.		• Patients aged nine years or older who are on or about to start puberty blockers or hormone treatment. • Patients over the age of 18 years about to undergo orchidectomy.	
Fertility Preservation for Transfeminine Adolescents Via Semen Cryopreservation or Testicular Sperm Extraction (TESE)	ClinicalTrials.gov ID NCT06400199	Recruiting	To identify and predict parameters for successful TESE procedures or semen cryopreservation more accurately and to evaluate the decision-making process and the experience of postponing or temporarily discontinuing puberty suppression to undergo successful fertility preservation.	Observational cohort	Transfemales: Adolescents with gender dysphoria aged 9–18 years.	Netherlands
Mental health and wellbeing						
Evaluation of the Effectiveness of Hormonal Treatment in Adolescents Suffering From Gender Dysphoria (TRANSADO)	ClinicalTrials.gov ID NCT06351501	Not yet recruiting	To assess the psychological benefits of starting gender-affirming hormones in early as opposed to late puberty.5	Multicentre randomised open trial with blinded assessment	• Experimental arm: Adolescents with confirmed gender dysphoria who are starting gender-affirming hormone treatment at 14 years (+/– 6 months); 4 years follow-up (to age 18). • Control arm: Adolescents with confirmed gender dysphoria who are starting gender-affirming hormone treatment at 16 years (+/– 6 months); 2 years follow-up (to age 18 years).	France

[5] Although this study does not assess GnRHa, it is a randomised trial assessing the impact of hormonal treatment started in early or late puberty and so it has implications for puberty blockade.

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