Servicio de Salud Metropolitano Sur Oriente
Región Metropolitana
Ministerio de Salud

COMPLEJO ASISTENCIAL
DR. SÓTERO DEL RÍO
JUNTOS PARA UNA MEJOR SALUD

Santiago 02 septiembre 2024

De: Equipo encargado del programa Identidad de Genero
CASR

A: Sergio Báez Vallejos
Director(S) Complejo asistencial Dr. Sotero del Rio

Junto con saludar; por medio de la resente, remito respuesta a solicitud de la cámara de Diputados de la República, Oficio 11-2024 de fecha 11 de septiembre del 2024, en el cual se solicita

La Comisión especial investigadora encargada de reunir informaciones relativas a determinados actos de Gobierno en relación con la ejecución de terapias y programas de acompañamiento de salud, psicológicos, educacionales, relacionales, sociales, judiciales y de cualquier otra índole, a sujetos cuya identidad de género no coincida con su sexo y nombre registral (CEI-57), acordó solicitar a ese Hospital, tener a bien, informar y remitir los estudios que se sirven de fundamento para sostener los índices de suicidalidad de los niños, niñas y adolescentes, con y sin tratamiento de bloqueadores de la pubertad, especialmente en el corto y mediano plazo.

Asimismo, interesa conocer el listado de personas que una vez realizado este tipo de procedimientos terminan con incapacidad laboral u otro tipo de condición.

Por último, remita el formato o modelo de autorización de consentimiento que permite acceder al Programa de Acompañamiento de la Identidad de Género (PAIG) y, también, a las terapias hormonales, en caso de corresponder.

Lo que tengo a honra poner en conocimiento de Ud., en cumplimiento del mencionado acuerdo y por orden de su Presidenta, diputada señora **Flor Weisse Novoa.**

Dios guarde a Ud.,

Desarrollo de las respuestas:

1. "***En relación a los estudios que sirvan de Fundamento para sostener los índices de Suicidalidad de NNA con y sin tratamiento de Bloqueadores de la pubertad".***

Respuesta:

Para fundamentar los índices de suicidabilidad en niños, niñas y adolescentes, se consideran los siguientes estudios:

- "Back to the future: is GnRha treatment in transgender and gender diverse adolescents only an extend evaluation phase?": Este estudio analiza los efectos a largo plazo del tratamiento con análogos de GnRH en adolescentes trans, sugiriendo que la intervención temprana puede ser beneficiosa para la salud mental y la reducción del riesgo suicida.

- "Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline": Esta guía establece recomendaciones para el tratamiento endocrino de personas con disforia de género, destacando la importancia de un enfoque multidisciplinario que incluya apoyo psicológico y social, lo cual puede impactar positivamente en la calidad de vida y en la disminución de riesgos asociados a la disforia.

- Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation: Examina la relación entre la supresión puberal y la ideación suicida, mostrando que los tratamientos pueden reducir significativamente el riesgo.

- Suicide-Related Outcomes Following Gender-Affirming Treatment: A Review: Revisión que destaca los resultados en términos de salud mental y tasas de suicidio después de tratamientos de afirmación de género.

- Review: Puberty Blockers for Transgender and Gender Diverse Youth – A Critical Review of the Literature: Un análisis crítico de la literatura sobre bloqueadores de pubertad y sus efectos en la salud mental y emocional de los jóvenes.

- Risk and Protective Factors for Self-Harm Thoughts and Behaviours in Transgender and Gender Diverse People: A Systematic Review: Este estudio identifica factores de riesgo y protección relacionados con el comportamiento autolesivo en personas trans y diversas en su género.

(se envía también en archivo adjunto)

2. ***En relación "al listado de personas que una vez realizado este tipo de procedimientos terminan en incapacidad laboral u otro tipo de condición"***

Respuesta: Al día de hoy. no tenemos antecedentes de Personas que les haya sucedido que durante o posterior a algún tratamiento de este tipo hayan sufrido de incapacidad laboral.

3. ***"En relación a : Remita formato o modelo de consentimiento que permita acceder al programa de Acompañamiento de identidad de Genero (PAIG) y también a las terapias hormonales, en el caso de corresponder"***

Respuesta: se adjuntan formatos de consentimientos y asentimientos respectivos.

- **Programa PAIG:**

Formulario de manifestación de voluntad de participar en el Programa de Acompañamiento para NNA trans y género no conforme hasta 9 años de edad

Documento adaptado desde Formulario Tipo Asentimiento Informado niños y niñas pequeños (< 13 años)[16]

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	Si tú manifiestas querer participar, le contaré de esto a alguno de tus cuidadores (o ambos) para que sepan. Ellos también podrán participar contigo, si quieren. Si tú no quieres participar, no hay problema, nadie te va a obligar ni se va a enojar.
En este Programa, distintos profesionales conversarán contigo para desarrollar herramientas que fomenten tu desarrollo integral, de acuerdo con tu identidad de género.	
	Tu participación es voluntaria durante todo el Programa. En cualquier momento puedes dejar de participar o no contestar preguntas. No tendrá ninguna consecuencia para ti, ni para tu familia, ni para tu jardín/colegio.

¿Te gustaría participar?			
	Sí _____		No _____

[16] Elaborado por el Comité de Ética de la Investigación de la Facultad de Ciencias Sociales de la Universidad de Chile. Disponible en elsiguiente enlace: http://www.facso.uchile.cl/facultad/presentacion/107053/comite-de-etica-de-lainvestigacion

Formulario de manifestación de voluntad de participar en el Programa de Acompañamientopara adolescentes trans y género no conforme, desde 10 años

Nombre del Establecimiento de Salud	
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Estoy en conocimiento de que puedo participar de un Programa de Acompañamiento para Niños, Niñas y Adolescentes Trans y Género No Conforme, el cual consiste en una orientación de distintos profesionales para poder desarrollar herramientas que fomenten mi desarrollo integral, de acuerdo con mi identidad de género.

Entiendo que mi participación en el Programa es de forma voluntaria y que, si acepto participar, pue-do dejar de hacerlo cuando yo lo desee.

- ○ SÍ, acepto participar del Programa de Acompañamiento
- ○ NO acepto participar del Programa de Acompañamiento

Se me ha explicado también que, debido a mi edad, además de manifestar mi voluntad, se requiere informar a mi Representante Legal. En caso de tener dos, se informará al que yo elija y se dejará re-gistro de esta acción en mi ficha clínica. Para esta información elijo a:

Nombre:_____

Datos de contacto: _____

Nombre de adolescente	
Nº ficha clínica	
RUN	
Fecha de nacimiento	
Firma	

Nombre profesional que aplica formulario	
Nº ficha clínica	
RUN	
Fecha de nacimiento	
Firma	

CONSENTIMIENTO INFORMADO PARA TERAPIA DE SUPRESION PUBERAL

En este documento de consentimiento informado se le entrega información a los padres o tutores legales acerca de los efectos esperados del tratamiento con análogos de GnRh y de sus riesgos, para que le ayude a decidir con el médico si es lo adecuado para su hijo (a). Léalo cuidadosamente y si tiene cualquier duda, consúltela al médico. Es importante que aclare todas sus dudas antes de tomar la decisión.

Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

La Hormona Liberadora de Gonadotropinas (GnRh) tiene un papel fundamental en el inicio de la Pubertad y en la mantención a través del tiempo de las características sexuales de la adultez, cuando se administran en forma externa una hormona similar llamada análogos de GnRH, detienen la producción de gonadotrofinas (LH y FSH) que son las hormonas que permiten que los testículos produzcan testosterona y los ovarios estradiol.

Los análogos de GnRH se inyectan vía intramuscular. Según la dosis las inyecciones pueden ser una vez al mes o cada 3 meses. En cualquier forma son muy eficaces para bloquear la producción de hormonas testosterona y estradiol.

El tratamiento con análogos de GnRh es reversible, por lo que, en caso de decidir suspenderlo, la pubertad se reanuda de forma habitual.

Efectos secundarios y riesgos de los Análogos de GnRH.

- Molestias locales en el sitio de inyección
- Reacción alérgica
- Dolor de cabeza
- Molestias digestivas, cambios en el apetito
- Irritabilidad, insomnio
- Dolores musculares
- Aumento del número de plaquetas en la sangre
- Puede haber disminución de la densidad mineral ósea (descalcificación de los huesos), por lo que se debe aportar suplementos de calcio y vitamina D.

Es muy importante que:

- Pregunte a su médico cualquier duda sobre este tratamiento o sobre las palabras que aparecen en este documento.
- No falte a los controles con su médico y haga todos los exámenes que le pida para detectar complicaciones y asegurar que el tratamiento sea eficaz y seguro.
- Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios causados por el análogo de GnRH.
- Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas o drogas ilícitas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento con análogos de GnRH.

Declaración de consentimiento.

Yo representante legal de mi hijo/hija; nombre _____
RUT_____, autorizo al Dr/Dra _____
de la Unidad de Endocrinología Pediátrica a iniciar el tratamiento de frenación del desarrollo puberal con análogos de GNRH a mi hijo o hija.
He sido informado sobre los efectos terapéuticos y efectos adversos de esta terapia, firmo esta declaración aceptando con conformidad los términos antes mencionados.

Firma del representante legal
Nombre _____

Firma Médico tratante
Nombre_____

Fecha _____

ASENTIMIENTO INFORMADO PARA TERAPIA DE SUPRESION PUBERAL

En este documento de asentimiento informado se le entrega información acerca de los efectos esperados del tratamiento con análogos de GnRh y de sus riesgos, para que le ayude a decidir con su médico si es lo adecuado para usted. Léalo cuidadosamente y si tiene cualquier duda, consúltela a su médico. Es importante que aclare todas sus dudas antes de tomar la decisión.
Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

La Hormona Liberadora de Gonadotropinas (GnRh) tiene un papel fundamental en el inicio de la Pubertad y en la mantención a través del tiempo de las características sexuales de la adultez, cuando se administran en forma externa una hormona similar llamada análogos de GnRH ,detienen la producción de gonadotrofinas (LH y FSH) que son las hormonas que permiten que los testículos produzcan testosterona y los ovarios estradiol.

Los análogos de GnRH se inyectan vía intramuscular. Según la dosis las inyecciones pueden ser una vez al mes o cada 3 meses. En cualquier forma son muy eficaces para bloquear la producción de hormonas testosterona y estradiol.
El tratamiento con análogos de GnRh es reversible, por lo que, en caso de decidir suspenderlo, la pubertad se reanuda de forma habitual.

Efectos secundarios y riesgos de los Análogos de GnRH.

- Molestias locales en el sitio de inyección
- Reacción alérgica
- Dolor de cabeza
- Molestias digestivas, cambios en el apetito
- Irritabilidad, insomnio
- Dolores musculares
- Aumento del número de plaquetas en la sangre
- Puede haber disminución de la densidad mineral ósea (descalcificación de los huesos), por lo que se debe aportar suplementos de calcio y vitamina D.

Es muy importante que:

- Pregunte a su médico cualquier duda sobre este tratamiento o sobre las palabras que aparecen en este documento.
- No falte a los controles con su médico y haga todos los exámenes que le pida para detectar complicaciones y asegurar que el tratamiento sea eficaz y seguro.
- Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios causados por el análogo de GnRH.
- Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas o drogas ilícitas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento con análogos de GnRH.

Declaración de asentimiento.

He leído este documento de asentimiento informado.

He recibido explicación del propósito, duración, efectos previstos y riesgos del tratamiento.

Mis preguntas han sido contestadas satisfactoriamente y entiendo la información que el médico me ha dado.

Por lo cual he decidido:

_____ Comenzar supresión puberal análogos GnRh

_____ No comenzar supresión puberal con análogos GnRh

_____

Nombre Firma

_____

Nombre del médico Firma

Fecha:

CONSENTIMIENTO INFORMADO PARA TRATAMIENTO HORMONAL DE MASCULINIZACIÓN.

En este documento de consentimiento informado se le entrega información acerca de los efectos esperados del tratamiento de masculinización y de sus riesgos, para que le ayude a decidir con su médico si es lo adecuado para su hijo. Léalo cuidadosamente y si tiene cualquier duda, consúltela a su médico. Es importante que aclare todas sus dudas antes de tomar la decisión, Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

La testosterona es la hormona que producen los testículos y se utiliza para masculinizar el cuerpo y reducir las características femeninas. La testosterona se usa en inyecciones intramusculares cada 2 a 4 semanas. Su médico determinará la dosis más adecuada para usted de acuerdo a sus necesidades, deseos personales y a su estado de salud. Cada persona responde de manera diferente a la testosterona y es difícil predecir las respuestas individuales. En algunas personas los cambios serán notorios, y en otras no tanto; al mismo tiempo, en algunas personas demorarán menos en aparecer y en otras más. Esto no depende de las dosis utilizadas, sino de otros factores como la sensibilidad individual a la hormona, la edad, el funcionamiento orgánico, etc.

Qué efectos podemos esperar del tratamiento con testosterona.

Los cambios masculinos en el cuerpo pueden tardar varios meses en empezar a aparecer y generalmente demoran de 3 a 5 años en completarse.

Algunos cambios serán PERMANENTES (no desaparecerán ni siquiera si suspende el tratamiento con testosterona) **y otros NO SON PERMANENTES** (probablemente se reviertan si suspende el tratamiento):

Cambios PERMANENTES
El tono de voz se volverá más grave
Crecimiento, engrosamiento y oscurecimiento de vello corporal y facial
Posible caída del cabello en las sienes y la corona de la cabeza (calvicie masculina)
Aumento en el tamaño del clítoris

Cambios No PERMANENTES
Ausencia de reglas
Posible aumento de peso
La grasa tiende a ir al abdomen y parte media del cuerpo (el cuerpo se ve más masculino)
Aumento de la masa muscular, la fuerza y sensación de más energía física.
Oleosidad de la piel, acné (que puede ser grave)
Tamaño de las mamas apenas disminuye, aunque pueden ablandarse
Aumento del deseo sexual
Cambios en el estado de ánimo; tal vez tenga reacciones menos emocionales y más sentimientos de frustración y enojo; posible aumento de la agresividad y menos control de los impulsos.

Posibles riesgos y efectos secundarios del tratamiento con testosterona:

• Pérdida de la fertilidad: tal vez no pueda embarazarse. Este efecto puede llegar a ser permanente después de un tiempo variable de tratamiento.
Sin embargo, la testosterona no es un método anticonceptivo eficaz. Usted podría embarazarse aun si no tiene reglas; si tiene relaciones sexuales y no quiere embarazo converse con su médico sobre el uso de algún método anticonceptivo
• Si se embaraza mientras usa testosterona, podría causarle daños al feto e incluso la muerte
• Sequedad vaginal con irritación y malestar vaginal; puede aumentar la susceptibilidad a las infecciones de transmisión sexual y por VIH.
• Pueden aumentar el colesterol, la presión arterial y el riesgo de ataques al corazón o cerebrales
• Puede aumentar el riesgo de desarrollar diabetes
• Mayor riesgo de apnea del sueño (problemas respiratorios mientras duerme)
• Alteraciones en exámenes de función del hígado. Algunas enfermedades del hígado pueden empeorar
• Aumenta el número de glóbulos rojos en la sangre (hematocrito), lo que podría llegar a causar problemas de coagulación o ataques cardíacos o cerebrales
• Mayor sudoración
• Pueden empeorar o aparecer dolores de cabeza y jaquecas
•Podrían empeorar algunas enfermedades mentales como el trastorno bipolar, la esquizofrenia y otros.

Es muy importante que:
• Evite fumar, porque aumenta los riesgos de este tratamiento.
• Use la testosterona sólo en la dosis y forma que su médico le recete. Usarla en dosis más altas que las recomendadas aumenta los riesgos y no funciona mejor para masculinizar al cuerpo; de hecho, las cantidades más altas de testosterona pueden convertirse en estrógenos, que van a interferir con la masculinización.
• Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas, drogas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento hormonal.
• Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios por la testosterona.
• Asista a sus controles regulares y hágase los exámenes que su médico le indicará, incluyendo Papanicolaou, exámenes pélvicos y mamografías, para detectar posibles complicaciones y asegurar que su tratamiento sea seguro y eficaz.

El tratamiento con testosterona es permanente. Usted puede parar el tratamiento en cualquier momento y por cualquier motivo. Es conveniente que consulte la decisión con su médico.

Su médico podría disminuir la dosis testosterona o podría dejar de recetarla por razones médicas y/o por motivos de seguridad; el médico le explicará los motivos de todas las decisiones de tratamiento.

Declaración de consentimiento.

He leído este documento de consentimiento informado. He recibido explicación del propósito, duración, efectos previstos y riesgos del tratamiento. Mis preguntas han sido contestadas satisfactoriamente y entiendo la información que el médico me ha dado.

Por lo cual he decidido:

_____ Comenzar terapia hormonal con testosterona

_____ No comenzar terapia con testosterona

Firma del representante legal _____

Nombre representante legal_____

Nombre del médico _____

Fecha: _____

ASENTIMIENTO INFORMADO PARA TRATAMIENTO HORMONAL DE MASCULINIZACIÓN.

En este documento de asentimiento informado se le entrega información acerca de los efectos esperados del tratamiento de masculinización y de sus riesgos, para que le ayude a decidir con su médico si es lo adecuado para usted. Léalo cuidadosamente y si tiene cualquier duda, consúltela a su médico. Es importante que aclare todas sus dudas antes de tomar la decisión. Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

La testosterona es la hormona que producen los testículos y se utiliza para masculinizar el cuerpo y reducir las características femeninas. La testosterona se usa en inyecciones intramusculares cada 2 a 4 semanas. Su médico determinará la dosis más adecuada para usted de acuerdo a sus necesidades, deseos personales y a su estado de salud. Cada persona responde de manera diferente a la testosterona y es difícil predecir las respuestas individuales. En algunas personas los cambios serán notorios, y en otras no tanto; al mismo tiempo, en algunas personas demorarán menos en aparecer y en otras más. Esto no depende de las dosis utilizadas, sino de otros factores como la sensibilidad individual a la hormona, la edad, el funcionamiento orgánico, etc.

Qué efectos podemos esperar del tratamiento con testosterona.

Los cambios masculinos en el cuerpo pueden tardar varios meses en empezar a aparecer y generalmente demoran de 3 a 5 años en completarse.

Algunos cambios serán PERMANENTES (no desaparecerán ni siquiera si suspende el tratamiento con testosterona) **y otros NO SON PERMANENTES** (probablemente se reviertan si suspende el tratamiento):

Cambios PERMANENTES
El tono de voz se volverá más grave
Crecimiento, engrosamiento y oscurecimiento de vello corporal y facial
Posible caída del cabello en las sienes y la corona de la cabeza (calvicie masculina)
Aumento en el tamaño del clítoris

Cambios No PERMANENTES
Ausencia de reglas
Posible aumento de peso
La grasa tiende a ir al abdomen y parte media del cuerpo (el cuerpo se ve más masculino)
Aumento de la masa muscular, la fuerza y sensación de más energía física.
Oleosidad de la piel, acné (que puede ser grave)
Tamaño de las mamas apenas disminuye, aunque pueden ablandarse
Aumento del deseo sexual
Cambios en el estado de ánimo; tal vez tenga reacciones menos emocionales y más sentimientos de frustración y enojo; posible aumento de la agresividad y menos control de los impulsos.

Posibles riesgos y efectos secundarios del tratamiento con testosterona:

• Pérdida de la fertilidad: tal vez no pueda embarazarse. Este efecto puede llegar a ser permanente después de un tiempo variable de tratamiento.

• Sin embargo, la testosterona no es un método anticonceptivo eficaz. Usted podría embarazarse aun si no tiene reglas; si tiene relaciones sexuales y no quiere embarazo converse con su médico sobre el uso de algún método anticonceptivo

• Si se embaraza mientras usa testosterona, podría causarle daños al feto e incluso la muerte

• Sequedad vaginal con irritación y malestar vaginal; puede aumentar la susceptibilidad a las infecciones de transmisión sexual y por VIH.

• Pueden aumentar el colesterol, la presión arterial y el riesgo de ataques al corazón o cerebrales
• Puede aumentar el riesgo de desarrollar diabetes
• Mayor riesgo de apnea del sueño (problemas respiratorios mientras duerme)
• Alteraciones en exámenes de función del hígado. Algunas enfermedades del hígado pueden empeorar
• Aumenta el número de glóbulos rojos en la sangre (hematocrito), lo que podría llegar a causar problemas de coagulación o ataques cardíacos o cerebrales
• Mayor sudoración
• Pueden empeorar o aparecer dolores de cabeza y jaquecas
•Podrían empeorar algunas enfermedades mentales como el trastorno bipolar, la esquizofrenia y otros.

Es muy importante que:

• Evite fumar, porque aumenta los riesgos de este tratamiento.
• Use la testosterona sólo en la dosis y forma que su médico le recete. Usarla en dosis más altas que las recomendadas aumenta los riesgos y no funciona mejor para masculinizar al cuerpo; de hecho, las cantidades más altas de testosterona pueden convertirse en estrógenos, que van a interferir con la masculinización.
• Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas, drogas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento hormonal.
• Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios por la testosterona.
• Asista a sus controles regulares y hágase los exámenes que su médico le indicará, incluyendo Papanicolaou, exámenes pélvicos y mamografías, para detectar posibles complicaciones y asegurar que su tratamiento sea seguro y eficaz.

El tratamiento con testosterona es permanente. Usted puede parar el tratamiento en cualquier momento y por cualquier motivo. Es conveniente que consulte la decisión con su médico.

Su médico podría disminuir la dosis testosterona o podría dejar de recetarla por razones médicas y/o por motivos de seguridad; el médico le explicará los motivos de todas las decisiones de tratamiento.

Declaración de consentimiento.

He leído este documento de consentimiento informado. He recibido explicación del propósito, duración, efectos previstos y riesgos del tratamiento. Mis preguntas han sido contestadas satisfactoriamente y entiendo la información que el médico me ha dado.

Por lo cual he decidido:

_____ Comenzar terapia hormonal con testosterona
_____ No comenzar terapia con testosterona

_____

Nombre Firma

_____

Nombre del médico Firma

Fecha:

COMPLEJO ASISTENCIAL DR. SÓTERO DEL RÍO
JUNTOS PARA UNA MEJOR SALUD

CONSENTIMIENTO INFORMADO PARA TERAPIA HORMONAL DE FEMINIZACIÓN

En este documento de consentimiento informado se le entrega información acerca de los efectos esperados del tratamiento de feminización y de sus riesgos, para que le ayude a decidir con su médico si es lo adecuado para su hija. Léalo cuidadosamente y si tiene cualquier duda, consúltela a su médico. Es importante que aclare todas sus dudas antes de tomar la decisión.
Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

Para feminizar el cuerpo se emplea estradiol que es la hormona que producen los ovarios. Además, se necesita bloquear la producción de testosterona (hormona masculina) por parte de los testículos para conseguir efectos satisfactorios. Esto se consigue con la administración de análogos de GnRH, medicamentos que detienen la producción de gonadotrofinas, que son las hormonas que permiten que los testículos fabriquen testosterona. Sin gonadotrofinas los testículos no funcionan.
El estradiol se usa por vía oral, el médico determinará la dosis, cada persona responde de manera diferente a las hormonas y es difícil predecir las respuestas individuales. En algunas personas los cambios serán notorios, y en otras no tanto; al mismo tiempo, en algunas personas demorarán menos en aparecer y en otras más. Esto no depende tanto de las dosis usadas, sino de factores personales.

Qué efectos podemos esperar del tratamiento con estradiol.

Los cambios femeninos en el cuerpo pueden tardar varios meses en empezar a aparecer y generalmente demoran de 2 a 5 años para completarse.

Cambios Permanentes (no desaparecerán si suspende el tratamiento)

- Crecimiento de mamas, que es variable de una persona a otra, pero generalmente es leve y puede ser asimétrico. No depende de la dosis de estradiol (mayores dosis no tienen un efecto mayor).
- Los testículos disminuyen de tamaño. Se atrofia la próstata.
- Disminución de espermatozoides y por ello infertilidad. Puede ser permanente después de 6 meses de tratamiento.

Cambios No Permanentes (probablemente desaparecerán si suspende tratamiento)

- Pérdida de fuerza y masa muscular
- Aumento de peso y acumulación de grasa en glúteos, caderas, cara, brazos y muslos.
- La piel se vuelve más suave. El acné disminuye.
- Vello corporal se vuelve más fino, más corto y crece más lentamente. El vello facial no siempre desaparece.
- La calvicie masculina no sigue aumentando, pero no vuelve a crecer cabello donde se perdió.
- Disminución del deseo sexual.
- Disminución de las erecciones hasta que desaparecen. El semen se vuelve más fluido y en menor cantidad.
- Puede que tenga reacciones más emocionales. Puede haber cambios en el estado de ánimo y pensamientos que dependen en gran medida de las características psicológicas previas de la persona.

Qué no cambiará con el tratamiento con estradiol: La estructura ósea de la cara y el cuerpo y la manzana de Adán. La voz cambia poco. Se requiere otro tipo de tratamiento para cambiarla.

Efectos secundarios y riesgos que puede tener el tratamiento con estradiol.

- Efectos poco frecuentes: náuseas y vómitos, especialmente al comenzar el tratamiento. Retención de líquido. Alteraciones en exámenes de función del hígado (generalmente leves)
- Formación de cálculos en la vesícula
- Infertilidad

- Aumento de prolactina (una hormona de la glándula hipófisis).
- Empeoramiento de la depresión.
- Aparición o empeoramiento de dolores de cabeza y jaquecas.
- Aumento del riesgo de tromboflebitis y tromboembolismo pulmonar o cerebral. Este riesgo es mayor en personas que fuman, que tienen más de 45 años, que tienen hipertensión arterial, colesterol alto, diabetes o antecedentes familiares de enfermedad cardiovascular.

En qué casos el tratamiento con estradiol está contraindicado.

En aquellas personas con alguna de las siguientes condiciones no se debe usar estradiol: antecedente de haber tenido enfermedad tromboembólica o alguna condición que favorezca su aparición; enfermedad coronaria o enfermedad o accidente cerebrovascular; hipertensión arterial no controlada; prolactina elevada; enfermedad grave del hígado; cáncer de mama o historia familiar de cáncer de mama; jaquecas o migrañas intensas; psicosis; insuficiencia renal; triglicéridos altos; diabetes mal controlada; obesidad mórbida.

Debe tener en cuenta que:

- Fumar aumenta considerablemente el riesgo de complicaciones graves por el uso de estradiol.
- Tomar estradiol en dosis más altas que las que indique su médico aumenta el riesgo de efectos secundarios y probablemente no produzca mejores efectos de feminización.
- Antes de cualquier cirugía debe suspender el tratamiento por algunas semanas.
- Su médico puede disminuir las dosis de estradiol o incluso suspenderlo por razones médicas y/o motivos de seguridad.

El tratamiento con estradiol es permanente. Usted puede decidir detener el tratamiento en cualquier momento y por cualquier motivo, pero es conveniente que consulte la decisión con su médico, para evitar posibles riesgos.

Es muy importante que:

- Pregunte a su médico cualquier duda sobre este tratamiento o sobre las palabras que aparecen en este documento.
- No falte a los controles con su médico y haga todos los exámenes que le pida para detectar complicaciones y asegurar que el tratamiento sea eficaz y seguro.
- Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios causados por el estradiol.
- Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas o drogas ilícitas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento con estradiol o los análogos de GnRH.

Declaración de consentimiento.

Yo representante legal de mi hijo/hija; nombre _____RUT_____, autorizo al ……..……. de la Unidad de Endocrinología-Pediátrica a iniciar terapia hormonal cruzada con estradiol a mi hija.
He sido informado sobre los efectos terapéuticos y efectos adversos de esta terapia, firmo esta declaración, aceptando con conformidad los términos antes mencionados.

Firma del representante legal _____
Nombre representante legal_____

Nombre del médico _____
Fecha: _____

COMPLEJO ASISTENCIAL DR. SÓTERO DEL RÍO
JUNTOS PARA UNA MEJOR SALUD

ASENTIMIENTO INFORMADO PARA TERAPIA HORMONAL DE FEMINIZACIÓN

En este documento de asentimiento informado se le entrega información acerca de los efectos esperados del tratamiento de feminización y de sus riesgos, para que le ayude a decidir con su médico si es lo adecuado para usted. Léalo cuidadosamente y si tiene cualquier duda, consúltela a su médico. Es importante que aclare todas sus dudas antes de tomar la decisión.
Usted tiene plena libertad para aceptar o rechazar el tratamiento y de suspenderlo en cualquier momento.

Para feminizar el cuerpo se emplea estradiol que es la hormona que producen los ovarios. Además, se necesita bloquear la producción de testosterona (hormona masculina) por parte de los testículos para conseguir efectos satisfactorios. Esto se consigue con la administración de análogos de GnRH, medicamentos que detienen la producción de gonadotrofinas, que son las hormonas que permiten que los testículos fabriquen testosterona. Sin gonadotrofinas los testículos no funcionan.
El estradiol se usa por vía oral y también se puede usar mediante aplicaciones en la piel (transdérmico). Su médico determinará la dosis y la vía de administración más adecuadas para usted de acuerdo a sus necesidades, deseos personales y a su estado de salud. Cada persona responde de manera diferente a las hormonas y es difícil predecir las respuestas individuales. En algunas personas los cambios serán notorios, y en otras no tanto; al mismo tiempo, en algunas personas demorarán menos en aparecer y en otras más. Esto no depende tanto de las dosis usadas, sino de factores personales.

Qué efectos podemos esperar del tratamiento con estradiol.

Los cambios femeninos en el cuerpo pueden tardar varios meses en empezar a aparecer y generalmente demoran de 2 a 5 años para completarse.

Cambios Permanentes (no desaparecerán si suspende el tratamiento)

- Crecimiento de mamas, que es variable de una persona a otra, pero generalmente es leve y puede ser asimétrico. No depende de la dosis de estradiol (mayores dosis no tienen un efecto mayor).
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- Aumento de peso y acumulación de grasa en glúteos, caderas, cara, brazos y muslos.
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- La calvicie masculina no sigue aumentando, pero no vuelve a crecer cabello donde se perdió.
- Disminución del deseo sexual.
- Disminución de las erecciones hasta que desaparecen. El semen se vuelve más fluido y en menor cantidad.
- Puede que tenga reacciones más emocionales. Puede haber cambios en el estado de ánimo y pensamientos que dependen en gran medida de las características psicológicas previas de la persona.

Qué no cambiará con el tratamiento con estradiol: La estructura ósea de la cara y el cuerpo y la manzana de Adán. La voz cambia poco. Se requiere otro tipo de tratamiento para cambiarla.

Efectos secundarios y riesgos que puede tener el tratamiento con estradiol.

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- Formación de cálculos en la vesícula
- Infertilidad
- Aumento de prolactina (una hormona de la glándula hipófisis).
- Empeoramiento de la depresión.
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- Aumento del riesgo de tromboflebitis y tromboembolismo pulmonar o cerebral. Este riesgo es mayor en personas que fuman, que tienen más de 45 años, que tienen hipertensión arterial, colesterol alto, diabetes o antecedentes familiares de enfermedad cardiovascular.

En qué casos el tratamiento con estradiol está contraindicado.

En aquellas personas con alguna de las siguientes condiciones no se debe usar estradiol: antecedente de haber tenido enfermedad tromboembólica o alguna condición que favorezca su aparición; enfermedad coronaria o enfermedad o accidente cerebrovascular; hipertensión arterial no controlada; prolactina elevada; enfermedad grave del hígado; cáncer de mama o historia familiar de cáncer de mama; jaquecas o migrañas intensas; psicosis; insuficiencia renal; triglicéridos altos; diabetes mal controlada; obesidad mórbida.

Debe tener en cuenta que:

- Fumar aumenta considerablemente el riesgo de complicaciones graves por el uso de estradiol.
- Tomar estradiol en dosis más altas que las que indique su médico aumenta el riesgo de efectos secundarios y probablemente no produzca mejores efectos de feminización.
- Antes de cualquier cirugía debe suspender el tratamiento por algunas semanas.
- Su médico puede disminuir las dosis de estradiol o incluso suspenderlo por razones médicas y/o motivos de seguridad.

El tratamiento con estradiol es permanente. Usted puede decidir detener el tratamiento en cualquier momento y por cualquier motivo, pero es conveniente que consulte la decisión con su médico, para evitar posibles riesgos.

Es muy importante que:

- Pregunte a su médico cualquier duda sobre este tratamiento o sobre las palabras que aparecen en este documento.
- No falte a los controles con su médico y haga todos los exámenes que le pida para detectar complicaciones y asegurar que el tratamiento sea eficaz y seguro.
- Informe a su médico de cualquier síntoma o problema médico nuevo que ocurra antes o durante el tratamiento o si cree que está teniendo efectos secundarios causados por el estradiol.
- Informe a su médico si toma o empieza a tomar otros medicamentos, suplementos dietéticos, hierbas o drogas ilícitas o alcohol, para que pueda explicarle las posibles interacciones y efectos que pueden tener en el tratamiento con estradiol o los análogos de GnRH.

Declaración de asentimiento.

He leído este documento de consentimiento informado.

He recibido explicación del propósito, duración, efectos previstos y riesgos del tratamiento.

Mis preguntas han sido contestadas satisfactoriamente y entiendo la información que el médico me ha dado.

Por lo cual he decidido:

_____ Comenzar terapia de feminización

_____ No comenzar terapia de feminización

_____

Nombre Firma

_____

Nombre del médico Firma

Fecha:

Saludos Cordiales

Equipo encargado del Programa de Identidad de Genero

Complejo asistencial Dr. Sotero del Rio

CC. Archivo

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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*Cosponsoring Associations: American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 24 July 2017. Accepted 24 August 2017.
First Published Online 13 September 2017

Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. **(*J Clin Endocrinol Metab* 102: 1–35, 2017)**

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)
1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)
2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕◯◯)
2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)
2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕◯◯).
2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)
2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)
3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕◯)
3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)
3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)
4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕◯◯)
4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕◯◯)
4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕◯◯)
4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕◯◯)
4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)
4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 |⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are "trapped" in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote "The Transsexual Phenomenon" (4), it was Hirschfeld who coined the term "transsexual" in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through "something in between" to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.

Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."

Gender-affirming (hormone) treatment: See "gender reassignment"

Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.

Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.

Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.

Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."

Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.

Gender variance: See "gender incongruence"

Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.

Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.

Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.

Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.

Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.

Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.

Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.

Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.

Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.

Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.

Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
   1. The condition exists with a disorder of sex development.
   2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
- the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
- gender dysphoria worsened with the onset of puberty,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
- the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

2. And the adolescent:
- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage $\geq$G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
- the persistence of gender dysphoria,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,

2. And the adolescent:
- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
- agrees with the indication for sex hormone treatment,
- has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 ⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕◯◯)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:
1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:
1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after "gender-reassignment surgery" (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (±1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (±1.4) years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (±2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog–treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D–deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog–treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 |⊕⊕◯◯)

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 |⊕⊕◯◯)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a] Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 l⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕◯◯)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕◯◯)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 |⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

Financial Disclosures of the Task Force*

Wylie C. Hembree (chair)—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Peggy T. Cohen-Kettenis**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Louis Gooren**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Sabine E. Hannema**—financial or business/organizational interests: none declared, significant financial interest or leadership position: Ferring Pharmaceuticals Inc. (lecture/conference), Pfizer (lecture). **Walter J. Meyer**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **M. Hassan Murad****—financial or business/organizational interests: Mayo Clinic, Evidence-based Practice Center, significant financial interest or leadership position: none declared. **Stephen M. Rosenthal**—financial or business/organizational interests: AbbVie (consultant), National Institutes of Health (grantee), significant financial interest or leadership position: Pediatric Endocrine Society (immediate past president). **Joshua D. Safer, FACP**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared. **Vin Tangpricha**—financial or business/organizational interests: Cystic Fibrosis Foundation (grantee), National Institutes of Health (grantee), significant financial interest or leadership position, Elsevier *Journal of Clinical and Translational Endocrinology* (editor). **Guy G. T'Sjoen**—financial or business/organizational interests: none declared, significant financial interest or leadership position: none declared.* Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

Acknowledgments

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Disclosure Summary: See Financial Disclosures.

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Heliyon 10 (2024) e26074

Contents lists available at ScienceDirect

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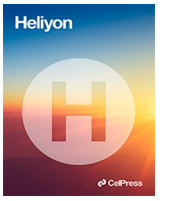

Review article

Risk and protective factors for self-harm thoughts and behaviours in transgender and gender diverse people: A systematic review

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ARTICLE INFO

Keywords:
Self-harm
Suicide
Risk factors
Protective factors
Transgender
Gender diverse

ABSTRACT

Background: Self-harm (any self-injury or -poisoning regardless of intent) is highly prevalent in transgender and gender diverse (TGD) populations. It is strongly associated with various adverse health and wellbeing outcomes, including suicide. Despite increased risk, TGD individuals' unique self-harm pathways are not well understood. Following PRISMA guidelines we conducted the first systematic review of risk and protective factors for self-harm in TGD people to identify targets for prevention and intervention.

Methods: We searched five electronic databases (PubMed, PsychInfo, Scopus, MEDLINE, and Web of Science) published from database inception to November 2023 for primary and secondary studies of risk and/or protective factors for self-harm thoughts and behaviours in TGD people. Data was extracted and study quality assessed using Newcastle-Ottawa Scales.

Findings: Overall, 78 studies published between 2007 and 2023 from 16 countries (N = 322,144) were eligible for inclusion. Narrative analysis identified six key risk factors for self-harm in TGD people (aged 7–98years) were identified. These are younger age, being assigned female at birth, illicit drug and alcohol use, sexual and physical assault, gender minority stressors (especially discrimination and victimisation), and depression or depressive symptomology. Three important protective factors were identified: social support, connectedness, and school safety. Other possible unique TGD protective factors against self-harm included: chosen name use, gender-identity concordant documentation, and protective state policies. Some evidence of publication bias regarding sample size, non-responders, and confounding variables was identified.

Interpretation: This systematic review indicates TGD people may experience a unique self-harm pathway. Importantly, the risk and protective factors we identified provide meaningful targets for intervention. TGD youth and those assigned female at birth are at increased risk. Encouraging TGD people to utilise and foster existing support networks, family/parent and peer support groups, and creating safe, supportive school environments may be critical for self-harm and suicide prevention strategies. Efforts to reduce drug and alcohol use and experiences of gender-based victimisation and discrimination are recommended to reduce self-harm in this high-risk group. Addressing depressive symptoms may reduce gender dysphoria and self-harm. The new evidence presented in this systematic review also indicates TGD people may experience unique pathways to self-harm related to the lack of social acceptance of their gender identity. However,

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https://doi.org/10.1016/j.heliyon.2024.e26074
Received 12 June 2023; Received in revised form 17 January 2024; Accepted 7 February 2024
Available online 14 February 2024

robust longitudinal research which examines gender-specific factors is now necessary to establish this pathway.

1. Introduction

Self-harm (defined here as any self-injury or -poisoning regardless of intent [1,2]) is an important public health concern [3] and is associated with various negative health and wellbeing outcomes. These include substance abuse [3,4], reduced education and employment [3] prospects, and exacerbating existing mental health issues [5]. Most concerningly, self-harm is the strongest known predictor of death by suicide [5]. Transgender and gender diverse (TGD) people are at significantly higher risk of self-harm compared to cisgender people [6,7]. Broadly, TGD describes people whose birth-assigned sex misaligns with their gender identity [8,9]. Cisgender (cis) describes people whose gender identity aligns with their birth-assigned gender and body [10]. Self-harm is highly prevalent in TGD people. Lifetime TGD self-harm prevalence estimates range between 46.4% [11,12] and 53.3% [13] compared to 6.4% in the general population [14]. Similarly, TGD people are at increased risk of suicidal thoughts [15] and behaviours [16]. Worryingly, almost 45% of TGD people attempt suicide [17], compared to 11.3% in the general population [18]. Furthermore, TGD people are at increased self-harm risk compared to their lesbian and gay peers. A recent meta-analysis reported TGD self-harm prevalence rates of 46.65% compared to 29.68% in sexual minority individuals [12]. The high prevalence of self-harm and adverse health and wellbeing outcomes indicate the need to understand TGD self-harm and identify key intervenable targets in this high-risk group.

As with the general population, TGD self-harm is muti-faceted and complex. However, TGD people experience a wider array of self-harm factors. Alongside risk factors for self-harm also experienced by the general population, such as hopelessness [19] and depression [3,20], TGD people also experience TGD-specific self-harm risk factors. For example, studies have identified experiences of transphobia [11], stigma [13,15], victimisation [4,7], and gender dysphoria [13] as significant correlates of self-harm in TGD peopleThese TGD-specific experiences may directly influence self-harm. They may also result in higher rates of depression, anxiety, or hopelessness which, in turn, might mediate the relationship between TGD-specific factors and self-harm [21]. Indeed, a longitudinal study of self-harm predictors in LGBT (Lesbian, Gay, Bisexual, and Transgender [20,22]) youth found hopelessness and depression fully or partially mediated the relationship between self-harm and LGBT victimisation, perceived family support, and conduct disorder [20]. Other studies report victimisation, prejudice, and discrimination, in particular, to be correlated with increased odds of negative mental health outcomes and self-harm in LGBTQ+ people [23–25]. While these findings relate to the wider LGBT population, they suggest efforts to reduce LGBT-specific risk factors, like victimisation, may reduce self-harm by reducing depression and hopelessness. This may also be the case with TGD people. Indeed, Price-Feeney et al. [25] suggest reducing TGD-specific factors (such as discrimination) is likely to reduce the disparity between self-harm and negative mental health experienced by TGD people.

Additionally, protective factors may mitigate TGD self-harm risk. Evidence suggests social and family support, reduced transphobia, TGD-safe schools or colleges, and having gender-appropriate documentation act as potential buffers against self-harm risk in TGD people [4,7,21]. Indeed, studies have found school and peer support were associated with reduced self-harm in both LGBT [16] and TGD [7] populations. Furthermore, these protective factors are also associated with reduced sexual and intimate-partner violence in TGD people [7]. Worryingly, TGD people experience high rates of these events [7], and they are known risk factors for self-harm in TGD people [4]. Therefore, efforts to increase support for TGD people in school and wider social contexts may provide a protective buffer against self-harm, and correlating risk factors. Similarly, other studies have found family [7] and parental [21] support and feeling connected to parents and non-parental adults [4] offered protection against self-harm outcomes. These protective factors may also have mediation effects on other protective factors. For example, having parents who are supportive of one's preferred gender may facilitate access togender-seeking surgery or obtaining gender-appropriate documentation [21],which, in turn, provide a buffer against self-harm. However, the literature regarding protective factors in TGD people is limited [4], therefore the protective impact of these, and other, protective factors on TGD self-harm is unclear. Simultaneously experiencing both general and TGD-specific risk factors may result in TGD people being at increased risk of experiencing self-harm [12,13]. Furthermore, interactions between risk and protective factors may result in a unique pathway to self-harm in TGD people [4]. Examining correlates of self-harm in TGD people is necessary to ascertain why TGD people are at increased risk of self-harming behaviours [12]. Synthesising extant literature and identifying key factors for TGD self-harm is important to identify meaningful and TGD-appropriate targets for intervention, develop interventions aimed at reducing self-harm prevalence [12], and develop intervention and support strategies which reduce self-harm in TGD and associated negative outcomes [12] in this high-risk group.

Previously, TGD self-harm has been researched under the LGBTQIA+ (Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, Intersex, Asexual, and other gender identities/sexualities [22]) umbrella [12,16,24]. This conflation is problematic as TGD people are often under-represented in these studies or TGD-specific data is not extractable [24]. Interventions targeting TGD people may be inadequate because factors influencing TGD self-harm differs from others within the LGBTQIA + umbrella. Indeed, research to better understand the distinct TGD self-harm pathway is essential and recommended by researchers in the field [4,25,26]. Others have provided reviews of self-harm in TGD people [6,27]. However, these reviews focus on prevalence rates rather than identifying factors which may provide important intervenable targets. A recent scoping review found promising evidence of the protective function of peer support against self-harm and suicide in TGD people [28]. However, self-harm pathways are complex and multifaceted. Currently, there is no systematic review of self-harm risk and protective factors in TGD people: the current review fills this gap in knowledge to inform TGD-specific research and interventions to increase understanding of the TGD self-harm pathway and increase wellbeing of this

high-risk group [26]. Identifying viable targets for intervention is key for researchers and clinicians [28].

1.1. Aims

Considering the paucity of research on risk and protective factors for self-harm in TGD populations our systematic review aims to critically examine and synthesise existing literature regarding risk and protective factors associated with self-harm in TGD people.

2. Method

2.1. Protocol and registration

This review was conducted in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guidelines (PRISMA [29,30]) and is registered on PROSPERO: CRD 42023396437. The protocol was developed in line with the Cochrane Handbook for Systematic Reviews [31].

2.2. Search strategy and selection criteria

Scoping searches identified relevant search terms and discussion between authors finalised search terms. Then, two authors (KB and LM) independently performed searches of PubMed, PsychInfo, Scopus, MEDLINE, and Web of Science databases. Searches were completed on November 6, 2023. Search terms included "self-harm", "non-suicidal self injur*", "suicid*", "trans*", and "gender divers*". Full search terms appear in Appendix 1. Studies were included if participants self-identified as TGD (including identities under that umbrella term; see Appendix 2.) with current or past self-harm and/or suicidality, and if they examined risk and/or protective factors for self-harm behaviours (see Table 1 for full inclusion/exclusion criteria). Eligible studies were imported into Endnote [32], the reference management system. Duplicates were removed, then studies were removed if they did not meet eligibility criteria. Titles and abstracts, and then full texts, were screened independently by two researchers (KB and LM). Independently, KB and LM extracted data, then cross-checked data extraction for accuracy. Extracted data included study details (author/s, date, study location), study design information (design type, recruitment method, self-harm outcome), participant characteristics (age, gender), measures used, and study findings. Discrepancies were resolved between KB and LM. Third author input was unnecessary.

2.3. Data synthesis

Search results are presented in Fig. 1. Due to significant heterogeneity of factors examined, we present a narrative synthesis of results of key risk and protective factors for TGD self-harm [6]. Study characteristics and findings were summarised in descriptive tabular format grouped by risk factors and protective factors, then further synthesised by TGD-specific and general factors.

3. Results

Of 8707 records identified, 8573 articles were screened by abstract. One-hundred and thirty-two articles had full texts screened. Overall, 78 studies were eligible for inclusion in this review (see Fig. 1 for PRISMA search results summary). A full list of excluded papers with reasons for their exclusion is available (see Appendix 3.)Full data extraction is available on request.

3.1. Study characteristics

Of 78 eligible studies, 68 were conducted in community settings, and 10 in clinical settings. Other key study (location, study design, risk and/or protective factors examined, self-harm outcomes, and key findings) and participant (*n*, gender identity, age-range, and

Table 1
Inclusion and exclusion criteria used in screening process.

Inclusion Criteria	Exclusion Criteria
English language peer-reviewed studies	Reviews, editorials, commentaries, or opinion pieces, grey literature, theses/dissertations, or conference proceedings
Any geographical location	Studies using parent/caregiver report
No start or end dates were used	Studies investigating self-harm or suicidality in TGD veterans or prison inmates
No age restrictions	
Only quantitative empirical studies	
Cross-sectional, longitudinal, cohort and mixed methods studies	
Measured outcome of self-harm (irrespective of suicidal intent), suicide ideation, and/or suicide attempt (attempt on own life or completed suicide)	
Studies must investigate risk and/or protective factors for self-harm in Transgender and Gender-Diverse (TGD) people	
Participants self-identifying as TGD (including diverse gender identities; see appendix 1	

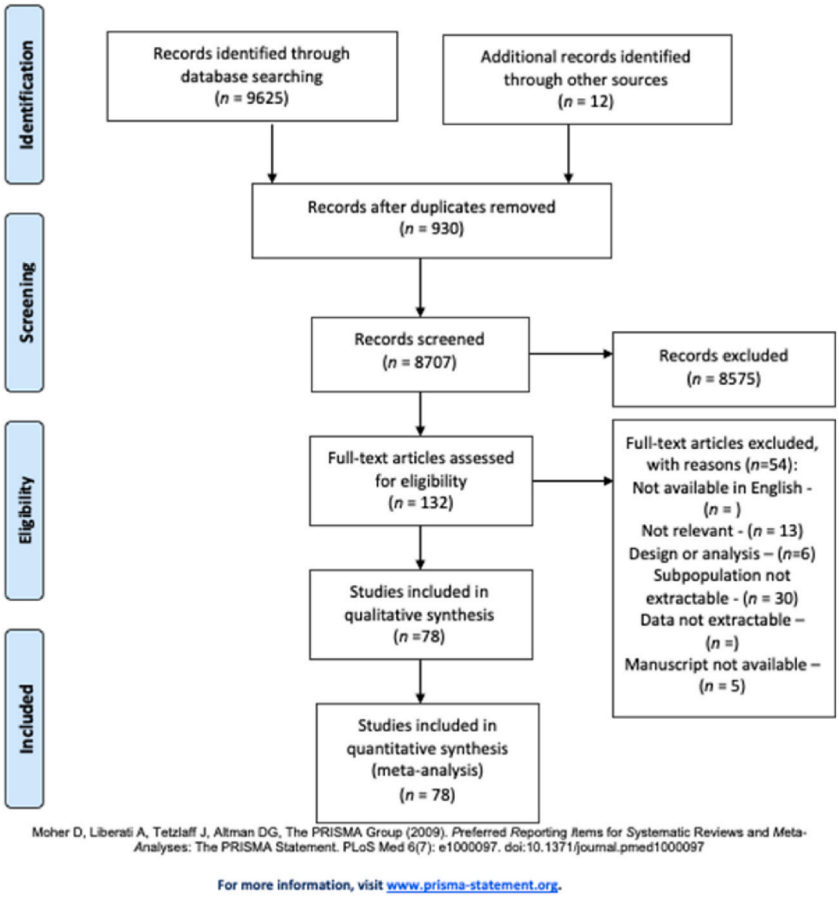

Fig. 1. Flow diagram illustrating literature search process.

mean ages) characteristics are presented in Table 2.

3.2. Sample characteristics

Participants included across studies totalled 322,144. Participant numbers in individual studies ranged from 16 to 27,715 (M = 4077.78, SD = 12,770). Ages ranged from 7- to 98-years. The combined mean age from studies, including participants' mean age at baseline, was M = 27.73(SD = 7.40). Other sample characteristics are included in Table 2.

3.3. Measures of risk and protective factors

Most studies used validated measures of risk and/or protective factors, though measures varied significantly. However, we found little evidence many measures were validated in TGD populations which may be problematic if they cannot sufficiently capture TGD specific issues [8]. For example, ten studies used the Patient Health Questionnaire (PHQ) for Depression [66,104,62,84,88,67,70,59,59,85] but there is no evidence PHQ is validated in TGD populations, meaning PHQ may not reliably assess depression in TGD people. This may be the case with other measures used by studies in this review. Some measures were validated in TGD populations, so are appropriate to capture TGD experiences. Perhaps unsurprisingly, these were TGD-specific measures (e.g., Gender Minority Resilience Model [39,67,91,79,43,51–53,59]; Transgender Congruence Scale [13,43]; Transgender Identity Survey [78]; Hamburg Body Drawing Scale [55,50]. See Table 2 for full list of risk and protective factor measures used across all studies.

3.4. Assessment of methodological quality

Bias risk and methodological quality were assessed using the Newcastle-Ottawa Scale adapted for cross-sectional studies [105], case-control and cohort studies [106]. These assess bias risk in three areas: participant recruitment/selection, participant comparability, and outcome. Studies are awarded a maximum of 9-(cohort and case-control) or 10-points (cross-sectional). Studies are rated high (7–10 points), moderate (4–6 points), or low. (0–3 points) quality. These quality categories have been used in previous systematic

Table 2
Summary of study and sample characteristic and findings.

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
Arcelus et al. (2016) [11] (UK)	Cross-sectional	$n = 268$ Natal female: 45.2% Natal male: 50.7% Did not answer: 4.1% Age range: 17–25 years (M = 19.9)	Demographics Psychopathology: SCL-90; Self-esteem: RSE; Transphobia victimisation: Experiences of Transphobia Scale; Interpersonal functioning: IIP-32; Social support: MSPSS	NSSI: SIQ	• Natal sex (female) & severity of clinical symptomology significantly associated with NSSI • Transphobia, low self-esteem & interpersonal problems significant predictors of psychopathology levels which is a risk factor for NSSI
Almazan et al. (2021) USA) [33]	Cross-sectional	$n = 27,715$ Trans woman: 38.3% Trans man: 29.1% Nonbinary: 30.2% Cross-dresser: 2.5% 18+ (not provided)	Demographics Severe psychological distress: K-6; Past-month binge alcohol use & past year tobacco smoking: all 1-item	Past-year suicide ideation & suicide attempt measure not provided	• Exposure to gender-affirming surgery significantly associated with reduced past-year suicide ideation, but not past-year suicide attempts • Participants with all desired surgeries had significantly reduced suicide ideation & attempts
Andrew et al. (2020) [34] (USA)	Cross-sectional	$n = 155$ Non-binary: 25.2% (no further breakdown provided) AFAB: 75.5% Age range not provided (M = 29.86)	Demographics Trauma exposure: Life Events Checklist; Nightmares: Trauma-Related Nightmare Survey; PTSD: PTSD checklist for DSM-5	Suicide risk: SBQ-R	• Nightmare frequency significantly associated with increased suicide risk • Nightmare severity was not significantly associated with suicide risk
Austin et al. (2022) [35] (USA & Canada)	Cross-sectional	$n = 372$ Trans man: 89.2% Non-binary/gender fluid: 32.8% Man: 9.4% Trans Woman: 11.6% Woman: 3.2% Demiboy: 1.1% Transgender: 0.3% Other: 0.8% Two-Spirit: 05% * **NB these categories are not mutually exclusive*** 14–18 years (M = 15.99)	Demographics LGBTQ-related stigma: 5-items from NHAI; Interpersonal & environmental LGBTQ microaggressions: Interpersonal LGBTQ Microaggressions subscale & Environmental LGBTQ Microaggressions subscale (adapted from LGBQ Microaggressions On-Campus Scale)	Suicidality: 2-items from DSM-5	• Interpersonal microaggressions significantly associated with suicide attempts • Familial emotional neglect, reduced school belonging & internalised self-stigma significantly associated with past 6-months suicidality • Reduced school belonging associated with past 6-months suicidality but not lifetime suicide attempts • Internalised stigma associated with suicide ideation but not suicide attempts
Azeem et al. (2019) [36] (Pakistan)	Cross-sectional	$n = 156$ Transgender Age range not provided (M = 39.26)	Demographics Depression: Hamilton Rating Scale for Depression Self-reported family income, illicit substance use and smoking: measures not provided	SI: Scale for Suicide Ideation	• Illicit substance use and depression significantly associated with suicide ideation • Age, smoking, and family income not significantly associated with suicide ideation
Barboza et al. (2016) [37] (USA)	Cross-sectional	$n = 350$ Transgender MTF: 62% FTM: 35% Age range not provided	Demographics Victimisation: 2 items; Substance use: 1 item covering 10 illicit substances; Family social support & Counselling or psychotherapy use: both 1-item	Suicidal Risk: 2 items	• Discrimination significantly associated with increased odds of suicide attempts • Non-discriminatory physical victimisation significantly associated with increased odds of suicide ideation & attempts • Being white, lower levels of perceived family support,

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					lack of psychological counselling/psychotherapy for TGD-related services, & past alcohol problems significantly associated with increased odds of suicide ideation& attempts • Housing instability significantly associated with increased suicide attempt risk • Higher education levels marginally associated with suicide ideation
Basar & Oz (2016) [38] (Turkey)	Cross-sectional	$n = 116$ Trans men: 75.9% Trans women: 24.1% Median: 25-years	Demographics Discrimination: PDS; Depression: BDI Resilience: RSA; Social support: MSPSS	Suicide attempt history; NSSI: ascertained by clinical interview	• Reduced resilience (lower RSA score) significantly associated with suicide attempt history but not NSSI
Bauer et al. (2016) [21] (Canada)	Cross-sectional	$n = 380$ Transgender MTF: 52.6% FTM: 47.4% 16+ (M = 32.7)	Demographics Chronic illness/pain, immigration history, religious upbringing, childhood abuse & mental health disorders: self-reported; Transphobia: Experiences of Transphobia Scale; Transphobic harassment & violence; medical transition status, hormone use, social transition status, being perceived as cisgender: self-reported; Social support: Medical Outcomes Study Social Support Scale	Past year suicide ideation & attempts: dichotomous scale	• Social support, reduced transphobia, medically transitioning though hormones/surgery, & having personal identification documents changed to appropriate/preferred sex were significantly associated with reductions in suicide risk • Parental support for gender identity was significantly associated with reduced suicide ideation • Lower self-reported transphobia associated with decrease in suicide ideation & suicide attempts • Religiosity & spirituality AND gender support from other sources except parents were not significantly associated with reduced suicidality
Brennan et al. (2017) [39] (USA)	Cross-sectional	$n = 83$ Trans women/MTF: 40% Trans men/FTM: 29% Various gender nonconforming identities: 31% 19–70 years (Not provided)	Demographics Depression: CES-D; Anxiety: Becks Anxiety Inventory; Gender Minority Stress: GMSR	Suicide ideation, suicide attempts & NSSI: dichotomous scale	• < 40 years more likely to have NSSI than >40 years • Distal stress (gender-related discrimination, gender-related rejection, gender-related victimisation, & non-affirmation of identity) weak positive predictor of suicide attempts • Resilience factors (pride & community connectedness) were marginal negative predictors of suicide attempt • Distal stress had weak positive relationship with suicide ideation • NSSI: age had moderate negative relationship • Suicide ideation: age had moderate positive relationship

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
Becerra et al. (2021) [40] (USA)	Cross-sectional	*n = 1369* Transgender 18+ (Not provided)	Demographics Psychological distress: K-6; Abuse/violence: 4-items; Partner abuse/violence: 24-items: Harassment/abuse due to bathroom use: 3-items	SI & SA: 4 questions with Y/N responses	• Abuse, violence, sexual partner abuse/violence are significantly associated with suicidal thoughts and behaviours • Harassment & abuse while using the bathroom is significantly associated with suicide attempts
Bosse et al. (2023) [41] (USA)	Cross-sectional	*n* = 286 Transgender and Nonbinary 18–25 years (M = 21.5)	Demographics Parental acceptance-rejection: Parental Acceptance-Rejection Questionnaire; Sibling acceptance-rejection: Elder Sibling Acceptance-Rejection Questionnaire; Depression: CES-D	Suicidality: 1 item for suicide ideation, planning & attempts	• No significant relationship between race, ethnicity, ASAB, whether living with parent & suicidality • Older age significantly associated with fewer lifetime suicide planning and attempts • Higher education significantly associated with fewer lifetime suicide plans and attempts & past year suicide ideation & attempts • Higher family rejection significantly associated with increased lifetime and past year suicidality • High sibling rejection was not associated with past year suicide attempts • Rejection from male parent particularly significant
Budhwani et al. (2018) [42] (Dominican Republic)	Cross-sectional	*n = 298* Transgender women Age range not provided (M = 26)	Demographics Sexual abuse, psychological abuse, torture, attempt on own life by another: dichotomous Y/N; Depression: 1 item; Illicit drugs: Dichotomous Y/N (in past 6-months); Income & education level: self-report	Suicide attempts: dichotomous Y/N	• Psychological abuse, torture & experiencing a murder attempt significantly associated with suicide attempt • Experiencing psychological abuse increases suicide attempt risk 3-fold • Experiencing torture or a murder attempt almost 3x more likely to attempt suicide • Depressed transgender women were 4x more likely to attempt suicide • Transgender women who used illicit drugs were 2x more likely to attempt suicide • Experiencing sexual abuse not associated with higher odds of suicide attempt compared to non-attempters • Low monthly income, age, & low education attainment not significantly associated with suicide attempt
Burish et al. (2022) [43] (USA & Canada)	Cross-sectional	*n* = 139 Transgender or nonbinary 18+ (M = 33.78)	Demographics Gender Minority Stress: GMSR Social Support: Perceived Social Support Scale from Family &	Suicidality: SBQ-R	• Optimism emerged as a significant protective factor • Body acceptance was a significant protective factor (and it predicted optimism)

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			Friends Scale; Optimism: LOT-R; Body Acceptance & Congruence: Transgender Congruence Scale		• Social support, community connectedness & pride were not significant protective factors
Busby et all. (2020) [44] (USA)	Cross-sectional	$n = 868$ (n = 86 identified as transgender) 18+ (Not provided)	Demographics Depression: PHQ-9; Discrimination: EDS; Interpersonal Victimisation: Interpersonal Victimisation Scale-Revised; Social Connectedness: UCLA Loneliness Scale; LGBTQ Affirmation: 3-items from LGBTQ Identity Affirmation Scale (modified from original 12-item scale)	Past year suicide ideation; lifetime suicide attempts; NSSI: 1 item from the Youth Risk Behavior Survey	• Victimisation, discrimination, connectedness, & LGBTQ affirmation were not significantly related to suicide and NSSI outcomes for transgender students • Some results were under wider LGBTQ umbrella so impossible to extract transgender-only data
Campbell et al. (2023) [45] (USA)	Cross-sectional	$n = 1078$ gender-conversion treatment $n = 24,192$ control Transgender 11–17 years when gender conversion efforts began (Not provided)	Demographics Gender conversion efforts: 1 item	Suicide attempts: dichotomous Y/N & number of attempts	• Exposure to gender conversion therapy is significantly linked with increased risk of SA in adolescents
Cerel et al. (2021) [46] (USA)	Cross-sectional	$n = 2784$ 27.3% transgender female 27% transgender man 38.7% non-binary 1.2% transgender unspecified 5.7% transgender other 18+ (M = 34.35 suicide exposure; M = 31.33: no suicide death exposure)	Demographics Suicide attempt exposure, support from family of origin, mental health diagnosis, being a POC, gender binary status & gender identity: all self-reported	Past year suicide ideation & attempts: 4-items with dichotomous Y/N	• Exposure to suicide attempts & suicide increases likelihood of recent suicide ideation, recent & lifetime suicide attempts, lifetime NSSI, & at least one current mental health diagnosis • Exposure to the suicide attempt of a TGD person increased suicide ideation but not suicide attempts • Exposure to suicide attempts & suicide more closely correlated with suicide ideation than suicide attempts • NSSI history, female natal sex, younger age, & lacking family support & exposure to suicide attempts & suicide were associated with suicide ideation & attempts • Being white, NSSI history, & lacking familial support differentiated those with suicide ideation from those with suicide attempt in peoople exposed to suicide attempt and suicide
Chen et al. (2019) [47] (China)	Cross-sectional	$n = 1309$ Transgender men: $n = 622$ Transgender women: $n = 687$ Age range not provided (Transgender men M =	Demographics Feelings towards natal sex, seeking hormone therapy, seeking gender reassignment surgery, intense conflicts with parents regarding	Self-harm, suicide ideation & suicide attempts measured using dedicated items (not specified)	• **Regarding suicide ideation:** • Transgender men: disliking natal sex, seeking gender reassignment surgery, depression, risk for major depressive disorder, self-

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
		3.78; Transgender women M = 22.89; Overall M = 23.31)	sexuality, discrimination or violence in public due to sexuality, childhood adversity (incl. Bullying and insults at school), Seeking MH support services & history of major depressive disorder: all measured using unspecified measures Depression: CESD-9; Self-esteem: RSE		harm, seeking mental health services all significantly predicted increased risk of suicide ideation • Transgender women: disliking natal sex, current or past major depressive disorder, depression, risk for major depressive disorder, self-harm, seeking mental health support services all significantly predict increased suicide ideation risk • ALL: disliking natal sex, seeking gender reassignment surgery, intense conflicts with parents, current or past major depressive disorder, depression, risk for major depressive disorder, self-harm, & seeking mental health services all significantly increased suicide ideation risk • **Regarding suicide attempts:** Transgender men: Experiencing violence and/or discrimination in public, current and/or past major depressive disorder & self-harm all significantly. Predicted increased suicide attempt risk • Transgender women: Being separated/divorced, current or past major depressive disorder, and self-harm all significantly predicted suicide attempt risk increase • ALL: Education level high school or equivalent, being married, being separated/divorced, intense conflicts with parents, self-harm & seeking mental health services all significantly predicted increased suicide attempt risk • No significant relationship between self-esteem, & self-harm & suicide
Chen et al. (2020) [48] (China)	Cross-sectional	$n = 250$ Transgender women 18+ (M = 27.9)	Demographics Anxiety & depression: K-10 Discrimination (incl. Verbal abuse), mental health status, PTSD screening, access to mental health services, alcohol & drug use, physical abuse, harassment (restricted personal freedom,	Suicide ideation & attempts: dichotomous Y/N	• Lack of residential status, bisexuality, homelessness before age 18, experiences of verbal, physical, or sexual violence, alcohol use, & severe mental health disorders were all significantly associated with suicide ideation & and prior suicide attempts • Moderate or severe psychological distress were

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			economic control due to gender identity), sexual violence: all dichotomous Y/N		associated with prior suicide attempts • Suicide ideation was strongly correlated with severe psychological distress • Moderate or severe psychological distress was significantly associated with prior suicide attempt
Chinazzo et al. (2023) [49] (Brazil)	Cross-sectional	$n = 213$ Transgender boys/men: 48.6% Transgender girls/women: 20.8% Non-binary: 30.7% 13–25 years (M = 18.53)	Demographics Depression: MDS; Discrimination: Lifetime & Daily Discrimination Subscale; Gender Distress: TYC-GDS; Socioeconomic Status: Deprivation Scale Social Support: MSPSS; Social Support relating to gender identity: 1 item; Gender Positivity: Gender Positivity Scale	Suicide ideation & attempts: dichotomous Y/N	• Socioeconomic deprivation & depressive symptoms significantly associated with suicide ideation & attempts • No significant relationship between discrimination & suicide ideation & attempts • Gender distress associated with suicide ideation (binary transgender people experience higher distress than nonbinary people • Gender positivity a significant protective factor & may counteract gender distress • Social support & support relating to gender were non-significant (friends' support for gender identity, affective support, positive social interaction support, and emotional/information support)
Claes et al. (2015) [50] (UK)	Cross-sectional	$n = 155$ Transgender men: $n = 52$ Transgender women: $n = 103$ 17–77 years (M = 34.52)	Demographics Psychological Symptoms: SCL-90-R; Body Dissatisfaction: HBDS; Transphobia/victimisation: Experiences of Transphobia Scale; Interpersonal Problems: IIP-32 Perceived Social Support: MSPSS; Self-Esteem: RSE	NSSI: SIQ	• NSSI significantly associated with younger age ($M_{age} = 26.98$ vs. $M_{age} = 38.91$) • Transgender males are significantly more likely to SH than Transgender women (57.7% vs 26.2%) • Psychological/clinical symptomology significantly associated with NSSI • Transgender women report lower self-esteem, but this is not significantly related to NSSI • Transgender women reported significantly more body dissatisfaction but not significantly related to NSSI • Transphobia, interpersonal problems not significantly related to NSSI • Trans people with NSSI reported finding it harder to be assertive & sociable & were more aggressive • Transgender men received more social support but not significantly related to NSSI, though people with

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					NSSI reported less family support • NSSI significantly associated with younger age, being male, and reporting more psychological symptoms
Cogan et al. (2020) [51] (USA)	Cross-sectional	$n = 155$ Various gender identities 18–67 years (M = 29.86)	Demographics Gender minority stress: GMSR; Traumatic experiences: Life Events Checklist for DSM-5	Suicide risk: SBQ-R	• Gender minority stressors (discrimination, gender-related rejection, gender-related victimisation, non-affirmation of gender identity, internalised transphobia, negative expectations of future events, concealment) and trauma are significantly associated with suicide risk • Community resilience specified in GSMR (community connectedness, pride) did not significantly mitigate suicide risk nor did it moderate relationships between stressors & risk
Cogan et al. (2021a) [52] (USA)	Cross-sectional	$n = 29.86$ Various gender identities 18–67 years (M = 29.86)	Demographics Traumatic experiences: Life Events Checklist; Gender Minority Stressors: GMSR	Suicide risk: SBQ-R	• Proximal stressors (internalised stress, internalised transphobia, negative expectations due to gender identity, concealment of gender identity) were all significant predictors of suicide risk • Sexual violence was a significant predictor of suicide risk
Cogan et al. (2021b) [53] (USA)	Cross-sectional	$n = 29.86$ Various gender identities 18–67 years (M = 29.9)	Demographics Lifetime Trauma Exposure; LEC-5; Distal gender minority stressors: GMSR	Suicide risk: SBQ-R	• Distal stressors (gender-related discrimination, rejection, victimisation & nonaffimation) were significantly associated with suicide risk & related to proximal stressors (internalised transphobia, negative expectations for future events, and concealment) • Proximal stressors (internalised stress, internalised transphobia, negative expectations due to gender identity, concealment of gender identity) also significantly related to suicide risk
Cramer et al. (2016) [54] (UK)	Cross-sectional	$n = 27,658$ Various gender identities 18+ (not provided)	Demographics Interpersonal correlates (HRD: family rejection, childhood harassment, rejection, discrimination); HRD in workplace, healthcare settings, health insurance; TGD-related	Suicidal thoughts & behaviours: 4-items with dichotomous	• Family rejection, childhood harassment, rejection & discrimination (HRD), workplace HRD, healthcare HRD & sexual assault were all significantly associated with suicide ideation & attempts

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			physical assault, lifetime TGD-related intimate partner abuse; sexual assault; connection to TGD community; family support & co-worker support: measures not specified		• Past year health insurance HRD, past year TGD-related physical assault & lifetime intimate partner violence were all significant associated with suicide attempts, but not suicide ideation • Family & co-worker support were significantly correlated with reduced suicide attempts, but not suicide ideation • Marginalized status (sexual, racial & disability linked to suicidal thoughts & behaviours risk • Discrimination & victimisation were significantly associated with past year suicide attempts • Being less out with TGD identity was a protective factor • Sexual minority, racial minority, lower education, lower income, military experience, disability status, & being uninsured were significantly associated with past year suicidal thoughts & behaviours risk
Davey et al. (2016) [55] (UK)	Cross-sectional	$n = 97$ Control: $n = 97$ 60 Transgender women 37 Transgender men Control: 60 cisgender women 37 cisgender men Age range not provided (Transgender: M = 36.18; Control M = 37.16)	Demographics, incl. Civil status, living situation TGD people were asked for treatment stage & hormone status; General Psychopathology: SCL-90-R Self-Esteem: RSE; Body Satisfaction: HBDS; Perceived Social Support: MSPSS	NSSI: SIQ-TR	• TGD group had significantly higher prevalence of current NSSI than control group • TGD men had significantly higher prevalence rates of current NSSI than TGD women • TGD NSSI group (TGD individuals reporting current NSSI) reported significantly higher psychopathology, lower self-esteem, lower body satisfaction & social support compared to the TGD no NSSI group & cisgender no NSSI group • TGD people with NSSI were significantly younger than both other groups (cisgender & TGD no NSSI)
de Graaf et al. (2020) [56] (Canada, UK, Netherlands)	Cross-sectional	$n = 2771$ Natal male: $n = 937$ Natal female: $n = 1834$ 13+ (M = 15.99)	Demographics, incl. age at assessment, year of assessment, full-scale IQ, parents' marital status, & parents' social class IQ: Wechsler Intelligence Scale for Children & Wechsler Adult Intelligence Scale; Parent social status/ education:	Suicidality = Item 18 from CBCL & Item 91 from YSR	• Natal sex (female) & behavioural & emotional problems were consistent predictors of suicidality across clinics & measures used • CBCL: Toronto-Amsterdam contrast: clinic, birth assigned sex, parents' marital status & social class, & general emotional &

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			Hollingshead's Four-Factor Index of Social Status (non-validated scale); Items from the CBCL & YSR were used to measure desire to be the opposite sex, poor peer relations & behavioural problems		behavioural problems were all significant predictors of suicidality • Toronto-London contrasts: clinic, birth assigned sex, & general behavioural & emotional problems were all significant predictors of suicidality • Amsterdam-London contrast: clinic, birth assigned sex, & general behavioural & emotional problems were all significant predictors of suicidality • YSR: Toronto-Amsterdam: birth assigned sex, poor peer relations, & general emotional & behavioural problems were significant predictors of suicidality • Toronto-London: clinic & behavioural & emotional problems were significant predictors of suicidality • Amsterdam-London: clinic & general behavioural & emotional problems were significant predictors of suicidality • Mixed findings regarding parent's marital status & social class depending on scale (results were significant on CBCL, but not for YSR)
dickey et al. (2015) [57] (USA)	Cross-sectional	$n = 773$ Various gender identities Age range not provided (M = 34.5)	Demographics Depression & Anxiety: DASS-21; Feelings about body: BIS	NSSI: ISAS	• Depression, anxiety & stress were significantly associated with NSSI • NSSI significantly associated with lower BIS scores (i.e., lower body image)
Drescher et al. (2021) [58] (USA)	Cross-sectional	$n = 70$ Transgender men: 43.4% Transgender women: 25.7% 4 Non binary: 40% 18-65 (M = 29.97)	Demographics Homelessness & perceptions about safety: 1-item (these were adapted from the LGBT Health & Services Needs in New York State study & Seattle LGBT Commission 2010 Needs Assessment Survey respectively) Physical violence & sexual violence victimisation: 3-items	Suicidality (ideation & attempts): Dichotomous Y/N	• Suicide ideation was significantly associated with history of sexual violence, homelessness, & perceived lack of CRSA safety (safety in local area) • Suicide attempts were significantly associated with sexual violence history, homelessness, & perceived lack of CSRA safety (safety in local area) • Partner violence was not significantly associated with suicide ideation or attempts • No demographic (age, gender identity, ethnicity, household income, education attainment level, & current financial situation) characteristics

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					were significantly associated with suicide ideation or attempts
Drescher et al. (2023) [59] (USA)	Cross-sectional	$n = 115$ Transgender Non-conforming 18+ (M = 27.61)	Demographic Depression: PHQ-9 Gender Minority Stressors/Resilience: GMSR Emotion Dysregulation; DERS-SF	Suicide intent & risk: SHI	• Emotion dysregulation was significantly correlated with suicide ideation, suicide attempts, suicide intent, and risk • Victimisation was significantly associated with suicide ideation, suicide attempts, suicide intent, and risk • Rejection was significantly associated with suicide ideation & suicide risk • Discrimination was significantly associated with suicide risk only
Edwards et al. (2012) [60] (USA)	Cross-sectional	$n = 106$ Transgender women: 40.6% Transgender men: 32.1% Questioning: 7.5% Genderqueer: 2.8% Nonbinary/gender fluid: 1.9% Neutrois: 0.9% Trans: 0.9% Intersex: 0.9% Not provided: 12.3% 18–65 years (M = 29.17)	Demographics Emotional Stability: Suicide Resiliency Inventory-25; Relational Support: Perceived Social Support from Family (PSS-FA) and Friends (PSS-FR)	Suicide risk: SBQ-R	• High levels of perceived support from friends & family significantly associated with their emotional stability which, in turn, was negatively associated with suicide risk • Participants with higher levels of support experienced increased emotional stability which led to lower suicide risk • Independently there was no relationship between perceived support & suicide risk
Goldblum et al. (2018) [61] (USA)	Cross-sectional	$n = 290$ Transgender 18–65 years (M = 37.01)	Demographics In-school gender-based victimisation: 2 items; Effect of gender-based victimisation: 1 item	Suicide attempt history: 2-item	• Younger age (<45) significant associated with suicide attempts • Transgender men significantly more likely to attempt suicide than transgender women • Ethnicity was significantly associated with suicide attempts • Multi-racial or 'other' were significantly more likely to attempt suicide, but White, African America, and Latina/o also reported high suicide attempt history • Higher socioeconomic status was significantly associated with reduced suicide attempts compared to lower & middle status • School-based gender-based violence was significantly associated with suicide attempts in transgender men and women
Gower et al. (2018) [62] (USA)	Cross-sectional	$n = 2168$ Natal female: 68.1% Natal male: 31.9% No age range provided but USA grades 5, 8, 9,	Demographics Parent connectedness: 3-item scale not validated; Youth Development Opportunities: 7-item	Suicide ideation and attempts: Dichotomous Y/N	• Feeling connected to parents was associated with significantly lower odds of suicide ideation and attempts

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
		11 (ages 10–18) (M not provided)	scale from Developmental Assets Profile; Teacher student engagement: 4-items from Student Engagement Inventory; Feeling safe in community: 2-item scale not validated; School safety: 1-item scale not validated; Depression: PHQ-2; Alcohol, drug, cigarette use in past 30 days: Dichotomous Y/N Single items measured how much you feel other adult relatives, friends, & adults in the community care about you		• An increase in connectedness results in a one-unit reduction in odds of suicide ideation and attempts • Having caring adults in the community & feeling safe at school were associated with significantly lower odds of suicide ideation and attempts
Green et al. (2021) [63] (USA)	Cross-sectional	$n = 11{,}914$ Nonbinary: 63% Trans male: 29% Trans female: 8% 13–24 years (M = 17.62)	Demographics Depression: PHQ; Victimisation, Receipt of puberty blockers, & exposure to GICE: all 1-item Gender-affirming hormone therapy: 3 items with binary responses; Parent support for gender identity: 2 items	Suicidal thoughts & behaviours: 2 items from YRB survey	• Receipt of gender affirming hormone therapy was associated with significantly lower odds of past year suicide ideation & attempts • Gender affirming hormone therapy also significantly associated with lower rates of depression
Grossman & D'Augelli (2007) [64] (USA)	Mixed methods	$n = 55$ Trans female: $n = 31$ Trans male: $n = 24$ 15–21 years (Trans female M = 17.5 Trans male M = 19.5)	Demographics Relation between suicide attempts & TGD status: RHAI; Lethality of suicide attempt determined by interviewer using lethality rating scale; Childhood Gender Nonconformity: GCS; Childhood Parental Abuse: Child & Adolescent Psychological Abuse Measure Body Esteem: Body-Esteem Scale for Adolescents & Adults	Suicide ideation: 3 items; Suicide attempts: Questions used in previous TGD suicide studies (cited) inc. whether drugs and/or alcohol was used at the time	• Childhood gender nonconformity was not significantly associated with suicide attempts • TGD-related suicide ideation, parental verbal abuse, parental physical abuse, lower body esteem (especially weight satisfaction & thoughts of how others evaluate one's own body) were all significantly associated with suicide attempts • Sexual minority status was significant factor for life-threatening behaviours in TGD youth
Grossman et al. (2016) [65] (USA)	Longitudinal (First panel data)	$n = 129$ MTF: $n = 44$ (34%) FTM: $n = 44$ (31%) MTDG: $n = 14$ (11%) FTDG: $n = 31$ (24%) 15–21 years (M = 18)	Demographics Painful & provocative events components of IPTS: PPES	Suicide ideation & attempts: 2 parts of SHBQ Suicide ideation components of IPTS: INQ Capacity for self-harm components of IPTS: ACSS	• **Regarding suicide ideation:** • FTM & FTDG experienced increased suicide ideation compared to MTF & MTDG • White Caucasian group reported greater suicide ideation than other racial groups but no significant differences between Hispanic & non-Hispanic groups • Suicide ideation lower in people who attended religious services

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					• Perceived burdensomeness & thwarted belongingness were independently significantly associated with suicide ideation • Only perceived burdensomeness was significant in full model • Acquired capability to enact was not significantly associated with suicide ideation, but painful & provocative events were associated with greater acquired capability for lethal self-harm • **Regarding suicide attempts:** • FTDG identity was significantly associated with suicide attempts • Non-Hispanic & Caucasian youth significantly associated with suicide attempts compared to Non-Hispanic & Black/African American youth • Frequent religious service attendance was associated with fewer suicide attempts • Suicide ideation & acquired capability for self-harm was significantly associated with increased suicide attempts • Thwarted belongingness & perceived burdensomeness were both significantly associated with suicide attempts • Painful & provocative events were significantly associated with suicide attempts • No significant interaction effects between perceived belongingness & painful/ provocative events or between perceived burdensomeness & thwarted belongingness • There was a significant interaction effect between thwarted belonginess & perceived burdensomeness & painful provocative events: thwarted belongingness had a significant positive association with suicide attempts only for those who experienced moderate amount of painful provocative events • Thwarted belonginess had no effect on those who

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					experienced almost no painful provocative events
Jackman et al. (2018) [13] (USA)	Cross-sectional (quantitative in-person interviews with survey)	$n = 332$ Transgender 16+ (M = 34.56)	Demographics Enacted stigma: EDS Felt Stigma: SCS; Transgender congruence: TCS Family support of TGD identity: 1-item; Friend support: 4-items from MSPSS; TGD community connectedness: 5-item subscale from GMSR	NSSI: SITBI	• Age, felt stigma, & trans congruence were significantly associated with past year self-harm • Each 1-year increase in felt stigma was significantly associated with an increase x 1 year was associated with a 2.33 increase in odds of past-year self-harm • Each increase of 1-year of age was associated with decreased odds of self-harm by factor of 3.23 • Enacted stigma & income were not significantly associated with increased past-year self-harm • Increase of one point on transgender congruence scale was associated with decreased odds of past-year self-harm by factor of 0.74 suggesting higher gender dysphoria levels associated with past year self-harm • Protective factors not significant
Kaplan et al. (2017) [66] (Lebanon)	Cross-sectional interview surveys	$n = 54$ Trans females 18–58 years (M = 27)	Demographics Depression: PHQ-& PHQ-9; General social support & social isolation: Items from Social Relationship Scale; Peer Support: 1-item regarding friends support of TGD identity; Gender identity openness: 2-items from RHS	Suicide ideation: 4-items; Suicide attempts: 2-items	• Suicide attempt history was significantly associated with lower general social support, lower social integration, lower peer support • Suicide attempt history was significantly associated with being more open about TGD identity in public & past or current hormone use • Depression was not significantly associated with suicide attempts. However, 55% of those who experienced a SA also experienced depression • History of sexual abuse & sex work was not significantly associated with suicide attempts • Education attainment, age, homelessness, & relationship status were not significantly associated with suicide attempts • Past & current hormone use were both significantly associated with suicide attempt history
Kaplan et al. (2020) [67] (Lebanon)	Longitudinal	$n = 16$ Trans women 22–50 years (Median = 26-years)	Demographics Sexual health & behaviour: 11-items measuring STI history; 13-items assessing sexual risk behaviour; & 23-	Suicidality: (thoughts, plans, & attempts ever & in past 3 months): Dichotomous Y/N	• Higher social cohesion was significantly correlated with reduced suicidal thoughts at 3-months post-test

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			items measuring sexual relationship power; Mental Health (Anxiety & Depression): HADS; Depression: PHQ-9; PTSD: 4-item Primary Care PTSD Screen Family acceptance: 9-item measure of family acceptance; Lifetime trauma: 25-item Trauma History Questionnaire; Social Support: Social Cohesion Scale; GMSR & MDPSS; Gender affirmation, identity & expression: TGD specific Multigroup Ethnic Identity Measure, 6-items measuring gender typicality, & Outness Inventory; 31-items measuring desire/satisfaction of transition; 22-items measuring gender affirmation; 5-items measuring gender affirmation satisfaction; War exposure: War Event Questionnaire; Transphobia: 35-item scale (validated in population)		• Increased community connectedness was associated with reduced depression • War event exposure was associated with higher anxiety
Klein & Golub (2016) [68] (USA)	Cross-sectional	$n = 3458$ Transgender & Nonconforming 19-98 (M = 36.69)	Demographics Substance misuse: Dichotomous Y/N; Family rejection: 7-items	Lifetime history of suicide attempts: Dichotomous Y/N	• Younger age, binary gender identity, non-white race/ethnicity, lower education & income, & being unemployed were all significantly associated with suicide attempt history • Family rejection also significantly associated with a history of suicide attempts • Relationship between substance misuse & suicide attempts was not measured
Kota et al. (2020) [69] (USA)	Cross-sectional	$n = 928$ Trans women 18–65 years (M = 35)	Demographics Perceived stigma: 4-items from RHM; Psychosocial impact of gender minority status: 4-items from TAIM; Depression: 6-items from BSI; Anxiety: 3-item subscale from BSI; Excessive drinking: 3-items; Non-inject drug use & Injection drug use: both 1-item; Intimate Partner Violence: 3-items; Sexual abuse: 3-items;	Suicide ideation: 2-items - 1 regards past-year suicide ideation & one whether this related to gender status	• 33% reported suicide ideation • Anxiety, perceived stigma of being transgender, the psychosocial impact of gender minority status, experiencing sexual abuse, family verbal abuse, & stranger verbal abuse were all significantly associated with higher odds of suicidal ideation • Partner support was a significant protective factor

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			Child Sexual Abuse: 1-item; HIV status: 1 item		
Kuper et al. (2021) [70] (USA0	Cross-sectional	$n = 1896$ Gender identity other than birth assigned sex: 78.1% AFAB 14-30 (M = −21.1)	Demographics Gender related affirmation: 7-items; Gender-related self-concept: 7-items; Victimisation (Gender & Sexual Orientation-related): 6-items; Desire for gender-affirming medical care: 1-item; Depressive symptoms: PHQ-9; Social Support: Friend & family support: MSPSS;	Past year suicide ideation, attempts & suicide risk: SBQ-R Past year suicide attempts: binary variable modified SBQ-R	• **Risk Factors:** Region of USA & race/ethnicity were not significantly associated with suicide-related outcomes • Gender identity & sexual orientation were significantly associated with suicide ideation, attempts & positive suicide risk score • Gender-related victimisation & depressive symptoms were independently associated with suicide ideation, attempts & positive suicide risk score • Gender-related self-concept negativity was positively associated with suicide ideation & attempts • Sexual orientation-related victimisation was positively associated with suicide attempts • Queer identity was positively associated with suicide ideation • Pansexuality was positively associated with suicide risk • **Protective Factors:** Age was negatively associated with suicide ideation & attempts • Male identity & friend support were negatively associated with suicide attempts (i.e., acted as protective factors) • Family support was negatively associated with suicide ideation
Leon et al. (2021) [71] (USA)	Retrospective clinical data	$n = 185$ AFAB: 86.6% AMAB: 13.4% 7–25 years (Median at clinic enrolment: 16.3; Median at most recent clinic visit: 18.6)	Demographics Social transition; Medical transition; Mental health history (diagnoses, history of suicide ideation & attempts, psychiatric hospitalisation, history of abuse, bullying & victimisation) all captured from electronic medical records	Documented in medical records	• Depression was significantly associated with NSSI • History of abuse (emotional, physical or sexual) was significantly associated with NSSI • Anxiety was non-significant • AFAB, transmasculine, mood disorder history, & abuse were significantly associated with NSSI • Age, race, ethnicity, social transition status, medical transition status, rural zip code residence, & nonmetro country residence were not significantly associated with a history of NSSI

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
Maguen et al. (2010) [72] (USA)	Cross-sectional	$n = 153$ Gender identity female: 25% Somewhat female: 20% Equally both: 25% Somewhat male: 24% Male: 6% 18+ (M = 47)	Demographics Mental Health Treatment: 3 items; TGD-related verbal abuse & physical violence: 2 items; IV drug use: 1 item;	Suicide attempts: Dichotomous Y/N & number of attempts	• Age & sex assigned at birth (female) were significantly correlated with past suicide attempts • Younger individuals were more likely to report attempted suicide • Psychiatric hospitalisation, ASAB (female) & TGD-related violence were all significantly associated with suicide attempts • Intravenous drug use was non-significant
Mak et al. (2020) [73] (USA)	Retrospective medical record	$n = 6327$ Trans men: 2875 (45%) Trans women: 3452 (55%) 3-45 (age groups: 3–17, 18–25, 26–35, 36–45, >45)	Demographics Mental health diagnoses as stated on EMR: incl. anxiety disorders, ADHD disorders, ASD, bipolar disorders, depressive disorders, schizophrenia spectrum disorders, substance use/abuse, conduct/disruptive disorders, eating disorders, dementia, other psychoses, & personality disorders	Suicide Attempts: Emergency Medical Records (as defined by ICD-9 or ICD10) Suicide Ideation: Binary variable: Ever or never	• Suicide ideation & attempts were 2–5 times higher for those with 1–2 mental health diagnoses • Suicide attempts were 7 times higher in those <18 than >45 years of age • Past suicide ideation & attempts were associated with 3 times increased likelihood of suicide attempts • No difference between trans men & and trans women regards suicide attempts
Maksut et al. (2020) [74] (USA)	Cross-sectional	$n = 381$ Trans women 15-29 (not provided)	Demographics Perceived, anticipated & enacted stigma (related to TGD status): Gender Identity Stigma Scale; Sexual behaviour stigma: Sexual Behavior Stigma Scale; Severe Psychological Distress: Kessler Scale	Suicide ideation & attempts: 1-item each	• Suicide ideation was significantly associated with lower income, bisexual, pansexual, queer & asexual sexualities • Suicide ideation was significantly associated with discriminatory comments from family, verbal harassment & family exclusion • Suicide ideation was significantly associated with being poorly treated in a healthcare facility, verbal harassment, & rape • Suicide attempts were significantly associated with younger age, not living in urban/suburban area (i.e., rural), rejection by friends, feeling unprotected by police, & avoiding healthcare services • Being poorly treated in a healthcare facility, being blackmailed, & hearing gossip from healthcare workers were significantly associated with suicide attempts
Marx et al. (2021) [75] (USA)	Cross-sectional	$n = 610$ Transgender & gender nonconforming 14–18 years (M = 15.81)	Demographics Sexual victimisation: 1-item; Sexual harassment victimisation: 1-item; Bias-based peer	Suicide ideation: 1-item	• Sexual victimisation, sexual harassment victimisation, drug use, & bias-based peer victimisation were all significantly associated with suicide ideation

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			victimisation: 1- item; Problematic drug use: 6-items Parental monitoring & support: 7-items; School belonging: 6-items		• School belonging & greater parental support were negatively associated with suicide ideation (i.e., are protective factors)
Moody & Smith (2013) [76] (Canada)	Cross-sectional	*n* = 134 Man/boy: 37.6% Woman/girl: (37.6% Trans: 50.4% Transgender (51.1% Transexual/ transsexual: 45.1% FTM: 27.1% MTF: 29.3% On FTM Spectrum:15% On MTF Spectrum:17.3% Genderqueer: 24.8% Two-spirit: 7.5% Transman: 24.8% Transwoman: 30.8%) Man of trans experience: 8.3% Woman of trans experience: 7.5% Androgyne: 8.3% Woman, boy, gender blender, bi-gender, polygender, pangender, cross-dresser, transvestite, intersexual, drag king: 30.4% Other (gender bent, third gender, gender fucker, trans woman):10.6% (participants may be in multiple categories) 18–75 years (M = 36.75)	Demographics Optimist; LOT-R; Social support: PSS-FR & PSS-Fa; Suicide resilience: SRI-25; Reasons for living; RFL	Suicidal behaviours: SBQ-R	• Perceived social support from family and friends, emotional stability, optimism, & child-related concerns (reason for living) were associated with lower suicidal behaviour scores indicating these factors provide some protection from suicidal thoughts and behaviours in TGD people • Emotional stability (part of suicide resilience) was found to be a significant protective factor • There were no significant differences in suicidal behaviours between FTM or MTF people
Parr & Howe (2019) [77] (USA)	Mixed-methods (Cross-sectional survey data included in this review)	*n* = 182 Trans female: n = 107 (26.6%)/Trans male: n = 75 (18.7)/ genderqueer/GNC: n = 44 (10.9%)/Other: n = 48 (11.9%) 14–65 years (not provided)	Demographics Identity nonaffirmation microaggression events: 3-items; Depression, acute sadness & loneliness: 2-items from SBQ-R	Past-year suicide ideation & lifetime suicide ideation & attempts: 2-items from SBQ-R	• A 1x unit increase in frequency of identity nonaffirmation microaggression events was significantly associated with 2.54x increased odds of past year suicide ideation or 3.20x increased odds of lifetime suicide attempts • A 1x increase in plausible values (as defined using latent logistic regression) reflecting TGD persons level of TGD identity was significantly associated with a 4.13x increase in odds of past year suicide ideation & 3.31x odds increase of lifetime suicide ideation or attempts • Each unit increase of identity nonaffirmation or denial microaggression events reported were

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					significantly associated with a 1.39x increased odds of past year suicide ideation when adjusted for events which didn't impact social engagement • A 1x increase in number of identity nonaffirmation events leading to feeling emotionally wearied or apathetic were significantly associated with a 21% increase odds of past year suicide ideation when adjusted for increases in events producing emotional pain • Increases in number of paining events were significantly associated with a 21% increase in odds of past year suicide ideation
Perez-Brumer et al. (2015) [78] (USA)	Cross-sectional	$n = 1229$ Transgender: FTM n = 532; MTF n = 697 (but included multiple gender identities) Age & mean not provided	Demographics Structural Stigma: 4-item composite index based on gender minority measure; Internalised Transphobia: Transgender Identity Survey	Lifetime & past-year suicide attempts: 2-items	• MTF trans identity, being white, college education or higher (compared to high school or less education) were all significantly associate with decreased odds of lifetime suicide attempts • Higher levels of internalised transphobia were significantly associated with increased odds of lifetime suicide attempts • College or higher education was significantly associated with decreased odds of past-year suicide attempts • Higher level of internalised transphobia was associated with past year suicide attempts, but not statistically significant • MTF identity, being white, & attaining college education or higher were all significantly associated with fewer lifetime suicide attempts • Lower levels of structural stigma were associated with decreased odds of lifetime suicide attempts
Peterson et al. (2017) [26] (USA)	Retrospective chart review	$n = 96$ MTF: $n = 54$ MTF: $n = 31$ Gender fluid/ nonbinary: $n = 15$ 12–22 years (M = 17.1)	Demographics Psychosocial assessment at outset appointment: drug/alcohol use; history of legal problems/arrest; gang involvement; involved in fights; history of being bullied; feel safe at home; interest in weight change: All dichotomous Y/N;	Suicide attempt history; cutting or self-injurious behaviour history: Dichotomous Y/N	• Older age was significantly associated with increased likelihood of suicide attempts • Drive for weight change (weight gain & weight loss) was significantly associated with suicide attempt history • Self-harm history was significantly associated with suicide attempts

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			Body image concerns: 1-item		• FTM identity (compared to MTF) were significantly more likely to have suicide attempt & self-harm history • Body dissatisfaction or body mass index (BMI) were not significantly linked to suicide attempts
Rabasco & Andover [79] (2020)	Cross-sectional	$n = 96$ Transgender woman: $n = 71$ Transgender man: $n = 26$ Gender nonconforming: $n = 8$ Gender queer: n = 9 Other: $n = 19$ 12–22 years (M = 17.1)	Demographics Minority stressors: GMSR; Gender Identity State Policy Score	Suicide ideation: BSS	• Victimisation & discrimination separately were statistically significant predictive of lifetime suicide attempts • Gender identity-specific state policies moderated victimisation & discrimination effects on suicide attempts: increased victimisation or discrimination increased suicide attempts at low level state policy but not medium or high levels • Fewer gender-affirmative state policies is significantly associated with increased discrimination & victimisation, & increased suicide attempts
Ross-Reed et al. (2019) [7] (USA)	Cross-sectional	$n = 858$ Natal male: $n = 453$ Natal female: $n = 435$ 11–19 years (not provided)	Demographics Sexual violence, dating violence, Dichotomous Y/N; Gender identity Y/N to either Cis or Gender Minority; 14 resiliency questions (family, peer, school, & community): 4-point Likert scale	NSSI & past-year suicide attempts: Dichotomous y/N	• Community support was non-significant in relation to NSSI and suicide attempts • Family support was significantly correlated with lower odds for suicide attempts & NSSI • Peer support was significantly correlated with NSSI
Russell et al. (2018) [44] (USA)	Cross-sectional	$n = 129$ Transgender Gender non-conforming 15–21 years (not provided)	Demographics Depressive symptoms: BDI for Youth; Chosen Name Use: Whether preferred name was different from name given at birth; Are you able to go by your preferred name at home; school; work with friends Social Support: CASSS	Suicidal Ideation & behaviour: SHBQ	• Chosen name use in more contexts predicted lower depression & reduced suicide ideation & behaviours - an increase of one context (home, work, school, with friends) predicted a 5.37 unit decrease in depressive symptoms, a 29% suicide ideation decrease & a 56% decrease in suicidal behaviour • Depression, suicide ideation & suicidal behaviour were lowest when chosen name was used in all 4 contexts
Scheim et al. (2020) [80] (USA)	Cross-sectional	$n = 22{,}286$ Trans woman: 35.6% Trans man: 33.1% Nonbinary AFAB: 25.5% Nonbinary AMAB: 5.8% 18+ (M = 30.9)	Psychological Distress: K-6 Gender concordant identification: 1 item	Suicide ideation: 3-items	• Participants with all identity concordant documents for preferred name & gender had lower prevalence of suicide ideation & planning (adjusted prevalence ratio

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					[APR] 0·78; 95% CI 0·72–0·85) • Having some (vs no) concordant documents were associated with small reductions in suicide ideation (APR 0·95; 0·91–0·98) & planning (APR 0·93; 0·86–1·00) • Participants with some or all gender identity concordant documentation were significantly less likely to attempt suicide than those with no documents
Seelman (2016) [81] (USA)	Cross-sectional	$n = 2325$ Trans male: 43.7% Trans female: 30.9% Gender nonconforming natal female:16.6% Gender nonconforming natal male: 2.2% Crossdresser male:4.7% Crossdresser female:1.9% 18–76 years (M = 31.02)	Demographics, incl. disability status Generation (time period) when participant attended college & age in college; Denial of bathroom access in college; Gender-appropriate housing in college (due to trans status); Interpersonal victimisation: experience of harassment/bullying; physical assault/attack; sexual assault by teachers/staff at school/ college due to trans status	Lifetime suicide attempts: Dichotomous Y/N	• Race, annual household income, physical or mental disability, being denied access to a school bathroom due to being transgender, being denied access to gender-appropriate campus housing due to being trans-gender were all signifi-cantly associated with lifetime suicide attempts • Being a TGD POC & having a physical or mental disability are all associated with suicide attempts • Denial of access to appropriate bathrooms & denial of access to appropriate campus housing were both significantly associated with lifetime suicide attempts • TGD people experiencing interpersonal victimisation (bullying, harassment, physical attack, sexual assault, harassment) from other students (but not teachers/staff) are 1.36x more likely to attempt suicide
Snooks & McLaren (2020) [82] (USA)	Cross-sectional	$n = 848$ Trans men: $n = 197$ Trans women: $n = 614$ 18–80 years (M = 26.27)	Demographics Gender affirming surgery: Y/N/I'd rather not say; Interpersonal Needs: INQ-R; Depression: CES-D	Suicidal thought & behaviours: SBQ-R	• Perceived burdensomeness significantly predicted suicidal thoughts & behaviours • Dispositional hope was a protective factor against suicidal thoughts & behaviours when perceived burdensomeness was lower, however not when perceived burdensomeness was higher
Staples et al. (2018) [83] (USA)	Cross-sectional	$n = 237$ Gender identity other: 55.9% FTM: 24.6% MTF: 10.2%	Demographics Distal TGD stress: Daily Heterosexist Experiences Questionnaire; Internalised TGD	Suicide ideation: BSS; NSSI: DSHI	• Race/ethnicity were not significantly associated with suicide ideation or NSSI • Visibility as TGD and degree of maleness/

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
		Nonbinary: 9.3% 18–44 years (M = 28)	negativity; transgender identity scale (TGIS)		femaleness were all significantly associated with NSSI & suicide ideation • Harassment and victimisation were both positively associatd with suicide ideation & NSSI • Internalised TGD-negativity was significantly associated with suicide ideation but not NSSI
Strauss et al. (2019) [84] (Australia)	Cross-sectional	$n = 859$ Transgender Gender diverse 14–25 years (M = 19.37)	Demographics Depressive Symptoms: PHQ-A; Anxiety: GAD-7; Self-reported psychiatric diagnoses, exposure to negative experiences, peer rejection, issues with educational setting, issues with accommodation, bullying, body dysphoria, discrimination, employment issues, experiencing significant loss, isolation from TGD people, isolated from services, helping others with mental health, lack of family support	Self-reported adverse health outcomes (incl. self-harm, suicidal thoughts & attempts - lifetime and past-year	• Factors significantly associated with lifetime desire to self-harm: Accommodation issues, bullying, discrimination, experiencing a significant loss, helping others with mental health issues, lack of family support, peer rejection, & school/university/TAFE issues • Factors not associated with desire to self-harm: Body dysphoria, employment issues, feeling isolated from not knowing TGD people, feeling isolated from services • Factors significantly associated with lifetime self-harm: Accommodation issues, bullying, discrimination, employment issues, experiencing a significant loss, feeling isolated from services, helping others with mental health issues, lack of family support, peer rejection, school/university/TAFE issues • Factors not associated with lifetime self-harm: Body dysphoria, feeling isolated from TGD people • Factors significantly associated with lifetime engagement in reckless life-endangering behaviours: Accommodation issues, body dysphoria, bullying, discrimination, employment issues, experiencing a significant loss, feeling isolated from services, lack of family support, peer rejection, school/university/TAFE issues • Factors not associated with lifetime engagement in reckless life-endangering behaviours: Feeling isolated from other TGD ppl, helping others with mental health issues

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					• Factors associated with lifetime suicide ideation: Accommodation issues, body dysphoria, bullying, discrimination, employment issues, experiencing a significant loss, feeling isolated from services, helping others with mental health issues, lack of family support, peer rejection. school/ university/TAFE issues • Factors not associated. with lifetime suicide ideation: Feeling isolated from other TGD people • Factors associated with lifetime suicide attempts: Accommodation issues, bullying, discrimination, employment issues, experiencing a significant loss, feeling isolated from services, lack of family support, peer rejection, school/university/TAFE issues • Factors not associated with lifetime suicide attempts: Body dysphoria & feeling isolated from not knowing other TGD people
Strauss et al. (2020) [85] (Australia)	Cross-sectional	*n* = 859 Transgender Gender diverse: 29.7% Trans men/men: 15% Trans women/women: 48.5% various nonbinary identities (incl. nonbinary trans masc, nonbinary transfemme, agender, bigender, pangender, and others) 14–25 years (M = 19.37)	Demographics Depressive symptom: PHQ-A (for adolescents); Anxiety: GAD-7; Self-reported psychiatric diagnoses: range of diagnoses listed (e.g., PTSD, eating disorders, substance use disorders) & *n* selected those which had received formal diagnoses; Exposure to abuse: various questions about negative experiences associated with poor mental health - 6 items	Self-harm & suicidal behaviours (self-harm ideation, self-harm, reckless behaviour endangering life, suicide ideation & suicide attempts): 5 items (3-point scale)	• Abuse (extrafamilial physical abuse, familial physical abuse, extrafamilial sexual abuse, intimate partner abuse other familial abuse (including emotional & verbal abuse & neglect)) were all significantly associated with self-harm & suicidal behaviours • Familial sexual abuse was significantly associated with suicide attempts & reckless behaviour which may endanger own life only
Suen et al. (2018) [86] (Hong Kong)	Cross-sectional	*n* = 106 Assigned male at birth: 63.2% Assigned female at birth: 38.8% 25->44 years (not provided)	Demographics Satisfaction with relationship status: Y/N; Quality of Life: 1-item- 6-point scale	Suicidality: 4-point scale -"never thought of suicide", "have had thoughts of suicide", "have often had thoughts of suicide", "have attempted suicide"	• Quality of life, age & monthly income together explained 15.8% of variance in suicidality • Quality of life was negatively & marginally significantly associated with suicide ideation (p = .058) • Age (15–24) was significantly associated with suicidality and were significantly more likely to report suicide ideation than >44 years (p = .041)

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					• Monthly Income (<HK $6000) was significantly associated with increased likelihood of suicide ideation • Reduced quality of life was significantly associated with suicide ideation compared to people without suicide ideation (p = .007) • Age, monthly income & quality of life combined explained between 15.8% & 22% of variance in suicide ideation depending on analysis • TGD people aged 15–24 years were more likely to report suicide ideation (p = .041) • Quality of life negatively predicted suicide ideation (p = .058)
Taliaferro et al. (2018) [87] (USA)	Cross-sectional	n = 2168 Transgender, genderqueer, genderfluid, or unsure about gender identity AMAB: 31.5% AFAB: 67.2% AFAB Declined to answer: 1.2% School grades 5, 8, 9, & 11 were given. These ages are 10–16 years (not provided)	Demographics Gender identity: Y/N beside relevant gender identity; Depressive Symptoms: PHQ-2; Gender- based bullying/ victimisation (2-items); Physical bullying/ victimisation: 1-item Parent connectedness: 3-items; Teacher/school adult relationships: Student Engagement Instrument: Friend caring: 1-item; Connectedness to non-parental adults: 2-items; School safety: item	Past year NSSI: How many times? >10 = repetitive	• Past year NSSI was significantly associated with depression & gender-based or physical bullying victimisation • Greater connectedness to parents & non-parental adults were significant protective factors • There was a significant interaction between non-parental adult connectedness & gender-based bullying victimisation: Those who reported such victimisation to non-parental adults were less likely to report NSSI • Depression was the most significant risk factor associated with repetitive NSSI • Parent connectedness & school safety were the most important protective factors to mitigate NSSI
Taliaferro et al. (2019) [88] (USA)	Cross-sectional	n = 1635 Transgender or gender nonconforming: AMAB: 32% AFAB: 68.1% 14/15 years & 16/17 years (not provided)	Demographics Assigned sex & gender identity: 2-items; Family substance use: 2-items; Physical health problems & mental health problems: both 1-item; Positive screen for depression: 2-items; Physical or sexual abuse: 3-items; Relationship violence, witness to family violence & teasing: all 2-items; Bullying: 4-items;	NSSI: 2-Item scale - 1 asking about past year NSSI engagement & how many times Suicide attempts: Ever attempted suicide, in past year, or no	• Being a natal female was significantly associated with increased likelihood of NSSI • People in Grade 9 (age 14/15) & receiving free/ reduced price lunches were more likely to report NSSI • Mental health difficulties, being a victim of teasing due to gender/gender expression, running away from home, & alcohol use were all significantly associated with NSSI (leading factors: mental

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			running away, violence perpetrator, skipped school, cigarette smoking, alcohol use, binge drinking: all 1-item Parent connectedness: 3-items; connectedness to other adults: 2-items; school engagement & teacher/school adult relationships: both 6-items; neighbourhood safety: 2-items; prescription drug misuse: 4-items; illegal drug use: 5-items; multiple sexual partners: 2-items; bullying perpetrator: 4-items; friend caring, sport participation, involvement in school activities, religious activities, physical activity, school plans, academic achievement, school safety: all 1-item		health problem, depressive symptoms, alcohol use) • No significant difference in NSSI by race/ethnicity or school location (city or other) • Long-term mental health problems, depression, running away, substance use were all significantly associated with experiencing both NSSI & suicide attempts • Physical or sexual abuse, relationship violence, bullying victimisation, less non-parental connectedness to adults, academic achievement, & marijuana use differentiated this group (NSSI & suicide attempts) from the NSSI only group: Leading factors were mental health problems, running away from home, lower levels of connectedness to non-parental adult, & marijuana use • Mental health problem, physical or sexual abuse, relationship violence, bullying victimisation, less parental connectedness, lower grades, lower levels of perceived school safety, & running away from home were all significantly associated with suicide attempts • Increased parental connectedness & school safety differentiated NSSI & suicide attempt group from NSSI only group
Tebbe & Moradi (2016) [89] (USA)	Cross-sectional	$n = 353$ Transgender (trans women, trans men, non-binary) 18–66 years (M = 25.21)	Demographics Prejudice & discrimination: DHEQ: Internalised antitrans attitudes: IHS; Fear of antitrans stigma: Gender-Related Fears subscale of Transgender Adaptation & Integration Measure; Drug use: Brief DAST; Alcohol use: AUDIT; Depressive symptoms: CES-D Social Support: Family, Friend, & Significant Other subscale of MSPSS	Suicide risk: SBQ-R	• Internalised anti-trans attitudes, drug use & depression all had a direct significant association with suicide ideation & attempts • Perceived discrimination, fear of anti-trans stigma, family support, significant other support, friend support, & alcohol use were not directly significantly related to suicide ideation & attempts • No difference by group (trans women, trans man, non-binary)
Testa et al. (2012) [90] (USA)	Cross-sectional	$n = 271$ Tran women: n = 179 Trans men: n = 92 18–69 years (M = 37)	Demographics Physical violence: 1 item, then 1 item regarding how many times these were gender-identity	Suicide ideation & attempts: Dichotomous Y/N & how many times	• Physical violence was significantly associated with suicide ideation in trans women but not trans men

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
			related; Sexual violence: 1 item, then 1 item regarding how many times these were gender-identity related; Alcohol abuse: Dichotomous Y/N; Illicit substance use: Dichotomous Y/N		• Physical violence was significantly associated with suicide attempts in trans men and trans women • Sexual violence was significantly associated with suicide ideation in trans men but not trans women • Sexual violence was significantly associated with suicide attempts in trans men and trans women
Testa et al. (2017) [91] (USA & Canada)	Cross-sectional	$n = 816$ Trans man; Trans woman; female to different gender; male to different gender; Intersex 18+ (M = 32.53)	Demographics External & internal gender minority stress: GMSR; Belongingness & perceived burdensomeness: INQ-121	Past year suicide ideation: SIS; Lifetime suicide ideation: 1-item; Lifetime suicide attempts: SA: 1-item	• Regarding Model 1 (GMSR): Indirect path of rejection to suicide ideation through internalised transphobia & negative expectations but not non-disclosure was significant • Indirect path from non-affirmation to suicide ideation through internalised transphobia & negative expectations but not through non-disclosure was significant • Internalised transphobia & negative expectations were significantly positively associated with suicide ideation, but non-disclosure was non-significant • Regarding Model 2 (IPTS): Examined associations between internal gender minority stressors & suicide ideation through perceived burdensomeness & thwarted belongingness: Model fit was excellent • Indirect path to suicide ideation through thwarted belongingness & perceived burdensomeness • Thwarted belongingness & perceived burdensomeness were each significant predictors of suicide ideation
Toomey et al. (2018) [92] (USA)	Cross-sectional	$n = 1773$ Trans female: $n = 202$ Trans male: $n = 175$ Nonbinary: $n = 344$ Questioning: $n = 1052$ 11–19 years (M = 14.7)	Demographics including highest parental education level, urbanicity, & gender identity	Lifetime suicide behaviour: Dichotomous Y/N 1-item: "Have you ever tried to kill yourself?"	• Nonheterosexuality, identifying as a racial/ethnic minority (non-White), older adolescents (age not specified) were all associated with higher odds of reported suicide behaviour • Higher parental education level & residing in urban spaces were significantly associated with lower odds of suicide behaviour • Within each gender identity group: Transgender adolescents: non-

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Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					heterosexual sexual orientation was associated with higher odds of suicide behaviour • For questioning adolescents: parent education (higher) was a protective factor • Trans adolescents identifying as bisexual, gay, or lesbian were associated with higher odds of reporting suicidal behaviour • No sociodemographic characteristics were significantly associated with suicidal behaviour in nonbinary adolescents
Treharne et al. (2020) [93] (Aotearoa/New Zealand & Australia)	Cross-sectional	$n = 700$ (TGD: $n = 293$; cisgender; $n = 308$) 18–74 years (M = 30)	Demographics Discrimination: EDS; Psychological Distress: K-10 Perceived social support: MSPSS; Resilience: BRS	Suicidal ideation: SIDAS Suicide ideation & attempts: Series of single items about suicidality; Self-harm: DSHI	• TGD people were significantly more likely to have lifetime suicide attempts compared to cis people • Younger age significant for cis but not TGD people • TGD people who live with people were 5x more likely to have suicide attempts than those who live alone • Discrimination was significantly associated with suicide attempts in TGD people compared to cis people • Distress was significantly associated with suicide ideation in TGD & cis people • Distress was significantly associated with suicide ideation & attempts in TGD people only • Higher social support was significantly associated with reduced self-harm in TGD people but not cis people • Higher resilience was a significant protective factor for cis people but not trans people
Trujillo et al. (2017) [94] (USA)	Cross-sectional	$N = 78$ Transmen: 33.3% Transwomen: 37.2% Another gender:29.5% 18+ (not provided)	Demographics Anti-trans discrimination: HHRDS; Depression & Anxiety: HSCL-25 Perceived social support: MSPSS	Suicidality: SBQ	• Anti-TGD discrimination was positively related to suicide ideation • Harassment & rejection were both positively associated with suicide ideation • Depression was a significant predictor of suicide ideation • Anxiety was not significantly related to suicide ideation or attempts

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					• Depression was a mediator between discrimination & harassment & suicide ideation • Social support from significant other (not from family or friends) moderated experiences of harassment & rejection with suicide ideation (so buffers impact)
Turban et al. (2019) [95] (USA, incl. Guam, American Samoa, & Puerto Rico & military bases)	Cross-sectional	*n* = *27,715* Crossdresser: 2.6% Trans woman: 63.4% Trans man: 21.1% Nonbinary/ genderqueer AFAB: 8.5% Nonbinary/ genderqueer AMAB: 4.5% 18->65 years (M = 31.2)	Demographics Lifetime exposure to GICE: binary Y/N; Experiencing GICE <10yrs; Binge Drinking during past month: >1 -day consuming >5 alcoholic drinks; Cigarette & illicit drug use (excl. marijuana); Psychological distress: K-10	Suicide ideation I in past year/SA requiring inpatient hospitalisation in past year; Lifetime suicide ideation & attempts	• 19.6% reported lifetime GICE exposure • Lifetime GICE exposure was significantly associated with severe psychological distress during previous month & lifetime suicide attempts • Recalled lifetime GICE exposure was also significantly associated with higher odds of lifetime suicide attempts • After adjusting for statistically significant demographics, GICE exposure <10yrs was significantly associated with increased odds of lifetime suicide attempts
Veale et al. (2017) [15] (Canada)	Cross-sectional	*n* = 923 Trans girls/women Trans boys/men Nonbinary AFAB Nonbinary AMAB 14–25 years (Not provided)	Demographics Enacted stigma: Enacted Stigma Index; Stress: Single items from General Wellbeing Schedule School connectedness: School Connectedness Scale; Family Connectedness: 7-items (non-validated); 19–25 yr olds were given 8-item Parent Connectedness Scale; Friend Support: 1-item; Social Support: 19–25 yr olds: Medical Outcomes Study Social Support Survey	Suicidality: NSSI, suicide ideation & attempts: Dichotomous Y/N	• Enacted stigma, discrimination, & harassment were all positive predictors of NSSI, suicide ideation & suicide attempts (especially for NSSI) • Social support was negatively associated with NSSI, suicide ideation & suicide attempts • For 14–18-year-olds: family connectedness was the strongest protective factor
Veale et al. (2021) [96] (Aotearoa/New Zealand)	Cross-sectional	*n* = 610 Trans and nonbinary 14–83 years (M = 32.1)	Demographics GICE: 1-item; Mental Health: K10; Family rejection: GMSR (1-item); Internalised transphobia: 3-items from Gender Identity Self-Stigma Scale	NSSI, suicide ideation & attempts: using questions from the NZ Youth 2000 series: No to more than 5 times (5-point scale)	• GICE exposure x 2 increased odds of NSSI & suicide ideation • GICE exposure was associated with 4x increased odds of suicide attempts
Wang et al. (2021) [97] (China)	Cross-sectional	*n* = 1293 Transgender & gender queer 13–29 years (M = 21.93)	Demographics Depression: CESD-9; Anxiety: GAD-7; Presence or absence of parental psychological abuse; Self-esteem: RES	Suicide & self-harm risk: 4-items	• Trans women were at increased suicide and self-harm risk compared to trans men & gender queer people • Parental abuse was significantly associated

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					with suicide & self-harm risk • Parental psychological abuse/neglect was significantly associated with risk of suicide & self-harm • Depression was significantly associated with self-harm & suicide in trans women & gender queer people
Woodford et al. (2018) [98] (USA)	Cross-sectional	$n = 214$ Transgender 18+ (M = 22.83)	Demographics LGBTQ interpersonal microaggressions & victimisation on campus (frequency): 7-items incl. bathroom use & being referred to as old/natal gender; Victimisation: Sexual Orientation Victimisation Questionnaire	Suicide attempts: 1-item	• TGD people reported significantly more suicide attempts than *cis*-LGBQ peers • Victimisation was significantly associated with TGD suicide attempts • Resilience was significantly associated with decreased odds of suicide attempt • TGD environmental & interpersonal microaggressions were not significantly related to suicide attempts • Pride & outness (with gender identity) were not significantly associated with suicide attempts
Yadegarfard et al. (2014) [99] (Thailand)	Cross-sectional (between groups)	$n = 260$ Trans women: n = 129 Cis men: n = 131 15–25 years (M = 20)	Demographics Family Rejection: 6-item measure designed for this study (no measure exists); Social Isolation: SSA; Loneliness: ICLA Loneliness Scale-Short; Depression: DASS-21 (short version); Sexual Risk Behaviour: 'series of questions'	Suicidal thoughts & attempts: PANSI	• Compared to cis people, TGD people reported significantly higher family rejection, lower social support, higher loneliness, higher depression, lower protective factors (PANSI-Positive) & higher negative risk factors (PANSI negative) related to suicide behaviour • Social Isolation was a significant predictor of TGD suicidal thinking
Yockey et al. (2020) [100] (USA)	Cross-sectional	$n = 790$ Transgender 18+ (not provided)	Demographics Interpersonal Violence: Y/N; Lifetime substance use (cigarettes, alcohol, vaping, & prescription drugs): 4-items Y/N	Suicidal Behaviours 3-items Y/N	• Gender, age, marital status, income, transgender status disclosure, & alcohol usage were all significantly associated with suicide ideation • Age, marital status, income, transgender status disclosure, & interpersonal victimisation were all significantly associated with suicide planning • Gender, victimisation, alcohol use, cigarette smoking, vaping, & use of illegal/prescription drugs were all significantly associated with suicide attempts

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
Yockey et al. (2022) [101] (USA)	Cross-sectional	$n = 27{,}715$ Transgender, nonbinary, genderqueer and others 18+ (not provided)	Demographics Psychological victimisation and harassment: 1 item Y/N; Family support: 1-item 3-point scale	Past year suicide ideation: 1- item Y/N	• Older age (25–44 & 65+) was significantly associated with decreased suicide ideation in the past year • Asian/Pacific Islanders reported decreased suicide ideation compared to White people • Lower income was significantly associated with increased suicide ideation • Gender identity (nonbinary/genderqueer) was significantly associated with increased suicide ideation • Having a neutral or unsupportive family was significantly associated with increased suicide ideation • Victimisation & violence were significantly associated with suicide ideation
Zeluf et al. (2018) [102] (Sweden)	Cross-sectional	$n = 796$ Trans feminine: 19% Trans masculine: 23% Gender nonbinary: 44% Transvestite: 14% Missing: 0.2% 15–94 years (not provided)	Demographics TGD-related victimisation: 3-items (not specified); Stigma: SCS; *Trans*-related healthcare issues; 2-items; Change of legal gender: 1-item; Illicit drug use & risky alcohol consumption: 1-item each Life Satisfaction: Life Satisfaction Scale; Social Support: 1-item; Practical support: 1-item; Openness with trans identity: not specified	Past year suicide ideation: Yes once; yes, several times; No Lifetime suicide attempts: Yes, between past 2 weeks & 1 year ago; yes, more than a year ago; No	• Unemployment or long-term sick leave, country of birth other than Sweden, & risky alcohol consumption were significantly associated with suicide ideation • Older age was significantly associated with decreased risk of suicide ideation (older age offers some buffering effect against suicide ideation) • After controlling for above covariates: Offensive treatment in past 3-months, lifetime exposure to TGD-related violence, less satisfaction with contacts with friends/acquaintances & less satisfaction with own psychological wellbeing were significantly associated with suicide ideation • Unemployment or long-term sick-leave, illicit drug use in past 6-months, & risky alcohol consumption were significantly associated with lifetime suicide attempts • After controlling for these variables: Offensive treatment in past 3-months, lifetime exposure to TGD-related violence & never having practical support remained significantly associated with lifetime suicide attempts

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Table 2 (*continued*)

Author/s & date (Location)	Study design	Participant characteristics	Outcome measures (Demographics, risk factors, protective factors)	Self-harm definition &measure	Key findings
					• TGD-related victimisation was significantly associated with suicidality despite access to gender-affirming healthcare • Protective factors: legal gender recognition & access to gender-affirming health-care were non-significant (though they measured desire to or whether it had begun, rather than completed medical transition) • There was no significant association between stigma & suicidality • There were no differences in suicidality between TGD experiences (identity) nor judicial status
Zwickl et al. (2021) [103] (Australia)	Cross-sectional	*n = 928* Trans male: 26% Trans female: 22% Gender non-binary: 14% Gender Queer: 4% Agender:2% Gender Fluid: 2% Gender Neutral: 1% Other - 3% 18–79 years (Median = 28 years)	Demographics Access to gender affirming hormones; access to gender affirming surgery; Access to trans support groups (Y/N/Unsure); Perceived discrimination from employment, housing, healthcare, &/or government services: items about different aspects of these factors; Self-reported depression diagnosis: Y/N; Physical assault: Y/N	Self-harm & suicide attempts: 1-item each Y/N/prefer not to say	• States of residence within Australia & locality (rural vs. metropolitan) were not significantly different in the proportion of suicide or self-harm • Unemployment, depression, desiring gender-affirming surgery in the future, history of physical assault, & institutional discrimination (incl. discrimination while accessing healthcare, including gender affirming healthcare), in employment, housing, & accessing gov services) were all significantly associated with increased odds of lifetime suicide attempts • Access to TGD support groups was not a significant protective factor • Being presumed male at birth was significantly associated with lower odds of lifetime suicide attempts • Physical assault was reported by 23% & was significantly associated with a 200% increase in lifetime suicide attempt odds • Unemployment was significantly associated with 55% higher odds of lifetime suicide attempts • Self-reported depression was significantly associated with 300% increased odds of suicide attempts • Not being able to access surgery was significantly associated with 73% increased odds of suicide attempts

Papers are ordered alphabetically.

Abbreviations:

ACSS = Acquired Capability Suicide Scale
ASAB = Assigned sex at birth
AUDIT = Alcohol Use Disorders Identification Test
BDI = Beck Discrimination Inventory
BIS = Body Investment Scale
Brief-DAST = Brief Drug Abuse Screening Test
BRS = Brief Resilience Scale
BSI = Brief Symptom Inventory
BSS = Beck Scale for Suicide Ideation
CAPA = Child & Adolescent Psychological Abuse Measure
CASSS = Child & Adolescent Social Support Scale
CES-D = Center for Epidemiological Studies Depression Scale
CBCL = Child Behavior Checklist
DASS-21 = Depression Anxiety Stress Scales
DHEQ = Modified Daily Heterosexist Experiences Questionnaire
DERS-SF = Difficulties in Emotion Regulation Scale-Short Form
DSHI – Deliberate Self-Harm Inventory
EDS = Everyday Discrimination Scale
FTDG – Female to different gender
FTM = Female to male
GAD-7 = Generalised Anxiety Disorder Scale
GCS = Gender Conformity Scale
GICE = Gender Identity Change Efforts
GMSR = Gender Minority Stress & Resilience Measure
HADS = Hospital Anxiety & Depression Scale
HBDS = Hamburg Body Drawing Scale
HRD = Harassment, rejection & discrimination
HRDS = Heterosexist, Rejection, & Discrimination Scale
HSCL-25 = Hopkins Symptoms Checklist-25
IHS = Internalised Homonegativity Subscale
IIP-32 = Inventory of Interpersonal Problems
INQ = Interpersonal Needs Questionnaire
INQ-R = Interpersonal Needs Questionnaire-Revised
ISAS = Non Suicidal Self-Injury and Inventory of Statements about Self-Injury
IPTS = Interpersonal Psychological Theory of Suicide
K-6 = Kessler Psychological Distress Scale-6
K-10 – Kessler Psychological Distress Scale-10
LEC-5 = Lifetime Events Checklist for DSM-5
LOT-R = Life Orientation Test-Revised
MTDG = Male to different gender
MDS = Modified Depression Scale
MSPSS = Multidimensional Scale of Perceived Social Support
MTF = Male to Female
NHAI = Nungesser Homosexual Attitudes Inventory
NSSI = Nonsuicidal Self-Injury
PANSI = Positive & Negative Suicide Ideation Inventory
PDS = Perceived Discrimination Scale
PHQ-9 = Patient Health Questionnaire
POC = Person of Colour
PPES = Painful & Provocative Events Scale
PSS-Fa = Perceived Social Support-Family
PSS-Fr = Perceived Social Support-Friends
PTSD = Post-Traumatic Stress Disorder
RFL = Reasons for Living Inventory
RHAI = Revised Homosexuality Attitude Inventory
RHM = Reactions to Homosexuality Measure
RHS = Reactions to Homosexuality Scale
RSA = Resilience Scale for Adults
RSE = Rosenberg Self-Esteem Scale
SBQ-R = Suicide Behaviors Questionnaire-Revised
SCL-90-R = Symptom Checklist 90-Revised
SCS = Stigma Consciousness Scale
SHBQ = Self-harm Behaviors Questionnaire
SHI = Self-Harm Inventory
SIDAS = Suicidal Ideation Attributes Scale
SITBI = Self Injurous Thoughts & Behaviors Interview
SIQ = Self-Injury Questionnaire
SIQ-TR = Self-Injury Questionnaire-Trauma Related
SRI-25 = Suicide Resilience Inventory-25
SS-A = Social Support Appraisals Scales
STI = Sexually Transmitted Infections
TAFE = Technical & Further Education
TAIM = Transgender Adaption & Integration Measure
TCS = Transgender Congruence Scale
TYC-GDS = Trans Youth CAN! Gender Distress Scale
TYC-GPS = Trans Youth CAN! Gender Positivity Scale
YRB = Youth Risk Behavior Survey
YSR = Youth Self Report

reviews of suicidality and SH [24,107]. Two reviewers (KB & LM) independently assessed methodological quality of studies and achieved full agreement. See Table 3 for assessment findings.

Thirty-six cross-sectional studies received a 'high' quality rating. The remaining thirty-seven were 'medium' quality, indicating some bias (results of quality assessment are presented in Table 2). Bias was associated in the following three areas. First, fifty-three studies omitted data comparing respondents and non-respondents, which is important to increase external validity of results [108]. Second, twenty-seven cross-sectional studies did not control for confounding variables. Future studies should control for covariates to ensure their impact on findings is understood and accounted for [109]. Finally, sixty-three studies did not justify sample size despite most having in excess of 200-participants. Including a power analysis would be an effective way for future studies to improve in terms of quality.

The case-control study [55] was rated 'high' quality where bias related to outcomes ascertained using self-report methods. Finally, the cohort study [67] received a 'medium' rating where bias related to a selective participant sample and not controlling for covariates. Three studies used medical records [26,108] or chart review [26] methods. No bias risk assessments exist for these methods, so quality assessment is not possible. However, as they provide valuable evidence regarding TGD self-harm, they were included. However, there are limitations to consider. For example, it is difficult to determine whether information was missed, misinterpreted, or mis-recorded by clinicians, which may impact our understanding as establishing causal relationships between factors and outcomes is difficult [110]. The heterogeneity of risk and/or protective factors investigated across eligible studies precludes meaningful results from a meta-analysis [111]. Consequently, a narrative synthesis was used to describe and summarise findings.

3.5. Risk and protective factors for self-harm and suicidality in TGD people

3.5.1. Protective factors

Overall, few studies examined protective factors for TGD self-harm.). The heterogeneity of protective factors investigated made it difficult to classify factors into domains. However, some themes were identified. These are social and/or family support,

Table 3
Results of the risk of bias and quality assessments.

Cross-sectional studies:

Author/s (Date)	Representativeness of sample	Sample size	Non-respondents	Risk factor measure	Comparability	Assessment of outcome	Statistical test	Quality rating
Arcelus et al. (2016) [11]	Y	Y		YY		Y	Y	Moderate
Almazan et al. (2021) [33]	Y		Y	Y	YY	Y	Y	High
Andrew et al. (2020) [34]				YY		Y	Y	Moderate
Austin et al. (2020) [35]	Y		Y	YY		Y	Y	Moderate
Azeem et al. (2019) [36]	Y		Y	Y	Y		Y	Moderate
Barboza et al. (2016) [37]	Y			Y	Y	Y	Y	Moderate
Başar & Öz. (2016) [38]	Y			YY		Y	Y	Moderate
Bauer et al. (2015) [21]	Y	Y		YY	YY	Y	Y	High
Becerra et al. (2021) [40]	Y			YY	YY	Y	Y	High
Brennan et al. (2017) [39]	Y			YY		Y	Y	Moderate
Bosse et al. (2022) [41]	Y		Y	YY	YY	Y	Y	High
Budhwani et al. (2018) [42]				Y	YY	Y	Y	Moderate
Burish et al. (2022) [43]	Y	Y	Y	YY		Y	Y	High
Busby et al. (2020) [104]	Y			YY	YY	Y	Y	High
Campbell et al. (2023) [45]	Y				YY	Y	Y	Moderate
Cerel et al. (2021) [46]	Y			Y		Y	Y	Moderate
Chen et al. (2019) [47]	Y			YY		Y	Y	Moderate
Chen et al. (2020) [48]	Y			YY		Y	Y	Moderate
Chinazzo et al. (2023) [49]	Y			YY		Y	Y	Moderate
Claes et al. (2015) [50]	Y			YY	Y	Y	Y	Moderate
Cogan et al. (2020) [51]	Y		Y	YY		Y	Y	Moderate
Cogan et al. (2021a) [52]	Y		Y	YY		Y	Y	Moderate
Cogan et al. (2021b) [53]	Y			YY	YY	Y	Y	High
Cramer et al. (2022) [54]	Y	Y		YY		Y	Y	Moderate
de Graaf et al. (2020) [99]	Y	Y		YY		YY	Y	High
dickey et al. (2015) [57]	Y			YY		Y	Y	Moderate
Drescher et al. (2021) [58]	Y			Y	YY	Y	Y	Moderate
Drescher et al. (2023) [59]	Y			YY		Y	Y	Moderate
Edwards et al. (2019) [60]	Y			YY	YY	Y	Y	Moderate
Goldblum et al. (2012) [61]	Y			Y	Y	Y	Y	Moderate
Gower et al. (2018) [62]	Y			YY	YY	Y	Y	High
Green et al. (2021) [63]	Y		Y	YY	YY	Y	Y	High
Grossman & D'Augelli (2007) [64]	Y			YY	Y	YY	Y	High
Grossman et al. (2016) [65]	Y			YY	YY	Y	Y	High
Jackman et al. (2018) [13]	Y			YY		Y	Y	Moderate
Kaplan et al. (2016) [66]	Y	Y		YY		Y		Moderate
Klein & Golub (2018) [68]	Y		Y	Y	YY	Y	Y	High
Kota et al. (2020) [69]	Y			YY	YY	Y	Y	High
Kuper et al. (2018) [70]	Y			YY	YY	Y	Y	High
Maguen & Shipherd (2010) [72]	Y			Y	YY	Y	Y	Moderate
Maksut et al. (2020) [74]	Y			YY	YY	Y	Y	High
Marx et al. (2019) [75]	Y	Y	Y	Y		Y	Y	Moderate
Moody & Smith (2013) [76]	Y			YY	YY	Y	Y	High
Parr & Howe. (2019) [77]	Y			YY	YY	Y	Y	High
Perez-Brumer et al. (2015) [78]	Y			YY	YY	Y	Y	High

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Table 3 (*continued*)

Cross-sectional studies:									
Author/s (Date)	Representativeness of sample	Sample size	Non-respondents	Risk factor measure	Comparability	Assessment of outcome	Statistical test	Quality rating	
Rabasco & Andover (2020) [79]	Y			YY	YY	Y	Y	High	
Ross-Reed et al. (2019) [7]	Y			YY	YY	Y	Y	High	
Russell et al. (2018) [44]	Y			YY	YY	Y		Moderate	
Scheim et al. (2020) [80]	Y		Y	YY	YY	Y	Y	High	
Seelman. (2016) [81]	Y		Y	Y	YY	Y	Y	Moderate	
Snooks & McLaren (2020) [82]	Y			YY	YY	Y	Y	High	
Staples et al. (2018) [83]	Y			YY	YY	Y	Y	High	
Strauss et al. (2019) [84]	Y			YY	YY	Y	Y	High	
Strauss et al. (2020) [85]	Y			YY		Y	Y	Moderate	
Suen et al. (2018) [86]	Y			Y		Y	Y	Moderate	
Taliaferro et al. (2018) [87]	Y			YY	YY	Y	Y	High	
Taliaferro et al., (2019) [88]	Y	Y	Y	Y	YY	Y	Y	High	
Tebbe & Moradi. (2016) [89]	Y		Y	YY		Y	Y	Moderate	
Testa et al. (2012) [90]	Y			Y	Y	Y	Y	Moderate	
Testa et al. (2017) [91]	Y	Y	Y	YY	Y	Y	Y	High	
Toomey et al. (2018) [92]	Y			Y	Y	Y	Y	Moderate	
Treharne et al. (2020) [93]	Y			YY	YY	Y	Y	High	
Trujillo et al. (2017) [94]	Y			YY		Y	Y	Moderate	
Turban et al. (2019) [95]	Y	Y	Y	Y	YY	Y	Y	High	
Veale et al. (2017) [15]	Y		Y	YY		Y	Y	Moderate	
Veale et al. (2021) [96]	Y			YY	YY	Y	Y	High	
Wang et al. (2021) [97]	Y			YY	YY	Y	Y	High	
Woodford et al. (2018) [98]	Y		Y	YY	YY	Y	Y	High	
Yadegarfard et al. (2014) [99]	Y			YY		Y	Y	Moderate	
Yockey et al. (2020a) [100]	Y		Y	Y	YY	Y	Y	High	
Yockey et al. (2022) [101]	Y		Y	Y	YY	Y	Y	High	
Zeluf et al. (2018) [102]	Y			YY	YY	Y	Y	High	
Zwickl et al. (2021) [103]	Y			Y		Y	Y	Moderate	
Cohort/Longitudinal studies:									
Author/s (Date)	**Representativeness of exposed cohort**	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Demonstration outcome of interest was not present at start of study**	**Comparability of cohorts on basis of design or analysis (Max 2*)**	**Assessment of exposure**	**Was follow-up long enough for outcomes to occur?**	**Adequacy of follow up of cohorts**	**Quality rating**
Kaplan et al. (2020)		Y	Y				Y	Y	Medium
Case-Control Studies:									
Author/s (Date)	**Case Definition Adequate**	**Representativeness of Cases**	**Selection of Controls**	**Definition of Controls**	**Comparability of cases & controls**	**Ascertainment of exposure**	**Same method for cases & controls**	**Non-response rate**	**Quality rating**
Davey et al. (2016)	Y	Y	Y	Y	YY		Y		High

NB. Ratings were in accord with the Newcastle-Ottawa Scales adapted for cross-sectional, case-control, and cohort & longitudinal studies.

connectedness, and school-related factors. Due to heterogeneity of remaining protective factors, they were classified as TGD-specific and general protective factors.

3.5.2. Social and/or family support

Thirteen studies found a significant correlation between social, and/or family support and reduced TGD self-harm and suicidality [21,66,62,102,67,69,99,70,76,37,54,75,93]. Ross-Reed et al. [7] also found family support correlated significantly with reduced suicide attempts and NSSI, though community and peer support were non-significant. Similarly, Trujillo and colleagues [94] found partner support moderated risk, but family/friend support did not. A further study found perceived social support significantly associated with emotional stability which, in turn, was negatively associated with suicide risk [60]. However, independently there was no relationship between social support and suicide risk. Both Zeluf et al. [102] and Yockey et al. [100] found receiving neutral or no support correlated with increased risk of self-harm, suggesting receiving positive social support may reduce risk. Only five studies reported non-significant findings [13,50,89,43,49], though participants with self-harm history in Claes and colleagues [47] study received less support than people without self-harm history. Overall, findings provide compelling evidence of the protective and mitigating nature of social support on TGD self-harm and suicidality and highlight the importance of TGD people having accessible avenues of support. Further, they align with findings from a recent scoping review examining the role of peer support in reducing TGD suicide risk [28].

3.5.3. Connectedness

Three studies found parental connectedness associated with significantly lower odds of self-harm and/or suicidality [4,62,88]. Two further studies found connectedness to non-parental adults a significant protective factor [4,88]. Brennan et al. [39] found community connectedness a marginally negative predictor of suicide attempts. However, two studies found no correlation [43,51]. Surprisingly, transgender community connectedness was non-significant [13]. Two studies investigated social connectedness with mixed results. One study each found social connectedness a non-significant [104] and significant [39] protective factor. 'Friend caring' was investigated by two studies. This was included as a connectedness factor in line with previous studies of self-harm in minority youth [112]. A study each found 'friend caring' significantly [4] and non-significantly [88] correlated with reduced self-harm and suicidality. Overall, evidence presented indicates connectedness may be an important protective factor against TGD self-harm and suicide risk.

3.5.4. School-related protective factors

Three studies found feeling safe at school significantly correlated with reduced suicidality [4,4,62]. The 1-item scale used to measure school safety was ambiguous, so it is unclear whether school safety relates to TGD-specific or general school safety. Additionally, its ambiguity possibly elicited participant responses which were either TGD-specific and general, or both, so further clarity here is important. School belonging was also a significant factor [75]. Other school-related factors investigated were teacher/school adult relationships [4,62,88], sports participation, and involvement with school activities [4]. Considering the protective nature of school safety there was, surprisingly, no correlation between these factors and reduced self-harm. Possibly, a safe school environment offers more protection than individual associated factors. Also, effects may be limited to students in these studies and further research may yield different results. However, the evidence presented here suggests ensuring a safe school environment for TGD students may provide a key self-harm and suicide prevention opportunity.

3.5.5. Risk factors

Investigated risk factors also varied greatly, however there was some homogeneity. These were assigned sex at birth (ASAB), age, race/ethnicity, income, education level, gender identity, and depression or depressive symptoms, drug and alcohol use, gender-minority stressors, victimisation, and discrimination. The remaining risk factors were investigated by fewer than five studies. These are listed in Table 1.

3.5.6. Assigned sex at birth

Eleven studies examined ASAB. Of these, eight found being assigned female at birth (AFAB) significantly correlated with lifetime and current NSSI/suicide attempts [4,11,84,56,50,71,72,46]. Additionally, Jackman et al. [13] found transgender men were significantly more likely to use NSSI to reduce 'bad feelings'. Given their identity, these participants were likely AFAB. Two studies found no significant correlation [86,41], while Zwickl et al. [103] reported being assigned male at birth was associated with lower odds of suicide attempts. Finally, one study [70] reported birth-assigned sex a significant predictor of suicide, though which birth-assigned sex was not clarified. However, overall, findings indicate TGD people AFAB are in particular need of support.

3.5.7. Age

Twenty-four studies investigated age as a risk factor. Six reported no significant correlation between age and self-harm and/or suicidality [78,66,102,71,36,93] and one [26] found older age associated with increased suicide attempts. The remaining studies found younger age significantly correlated with self-harm and/or suicidality [13,92,39,55,73,86,42,50,70,74,41,61,68,72,46,100,101]. This is in line with evidence regarding self-harm/suicidality in the general population [5] and highlights the need for interventions targeting young TGD people.

3.5.8. Depression or depressive symptoms

Nineteen studies investigated depression or depressive symptoms. Seventeen reported a significant correlation between depression

or depressive symptoms and self-harm and/or suicidality [4,11,84,88,94,42,48,103,99,47,70,89,71,36,49,57,97]. Two reported no correlation [66,69]. However, one of these [66] reported 55% of participants with suicide attempt history also experienced depressive symptoms suggesting a possible relationship. Overall, these findings indicate depression and depressive symptoms are a significant risk factor for self-harm and suicidality and are a key intervenable target.

3.5.9. Physical and sexual assault

Both sexual assault/rape [74,52,54,75,85,90,58] and physical assault [4,81,88,103,48,71,40,85,90,100] are strongly correlated with TGD self-harm. All studies examining these factors recorded significant results. These results are deeply concerning but unsurprising considering TGD people experience high rates of both sexual and physical violence [90]. Supporting TGD who experience physical or sexual assault is likely to be an essential self-harm reduction strategy and will reduce the wider negative impact on mental health and wellbeing.

3.5.10. Illicit drug and alcohol use

In total, four [102,48,37,100] of six [102,48,69,89,37,100] studies reported alcohol use associated with self-harm. Similarly, six [102,42,89,36,75,100] of eight [102,42,69,89,36,72,75,100] studies found illicit drug use correlated with self-harm. These findings are in line with the general population [89] and strongly indicate reducing drug and/or alcohol use is likely to be important in reducing self-harm risk in TGD populations. Drug and alcohol use may also be linked to other mental health outcomes and self-harm risk factors [62,42]. Therefore, identifying whether drugs and/or alcohol are being utilised and addressing their use may have wide-reaching health and wellbeing benefits for TGD people.

3.5.11. Gender-minority stressors

All seven studies [39,70,79,91,37,52,53] examining gender-minority stressors reported significant relationships with self-harm and suicide-related outcomes. Six used the Gender-Minority Stress-Resilience Measure which examines the impact of proximal (internalised transphobia, negative expectations of future events, concealment of gender identity) and distal (gender-related discrimination, rejection, victimisation, non-affirmation of gender identity) stressors. Two studies reported distal stressors were significant predictors of suicide ideation, attempts, or risk [39,53] and were associated with proximal stressors [53]. However, one was a weak predictor [39]. Two of the studies reported proximal factors were significant predictors of suicide risk [52,53]. Other studies focused on the individual stressors of gender-related victimisation [70,79,37] and discrimination [37] which were all significantly associated with suicide ideation and attempts. Finally, Testa et al. [91] found an indirect path between rejection and suicide ideation through internalised transphobia and negative expectations, and an indirect path between identity non-affirmation to suicide ideation through internalised transphobia. Further, they found both internalised transphobia and negative expectations were significantly correlated with suicide ideation. Identity nondisclosure, however, was not significant in any pathway.

Overall, sixteen studies examined discrimination as a distinct risk factor. Two found no correlation[43,66.] However, fourteen reported a significant correlation between discrimination and self-harm [15,39,84,94,103,47,91,79,74,37,49,54,59,93]. A further study did not investigate a correlational relationship but reported TGD people experienced high levels of discrimination. The authors state this is the primary reason for mental health difficulties in TGD people [48], a notion supported by others [94]. As a distinct factor, victimisation was examined by eleven studies. Of these, ten reported a significant correlation between victimisation and self-harm [88,102,91,40,54,61,75,83,98,100], and only one [104] reported no correlation. Thefindings presented here suggest gender-minority stressors, particularly victimisation and discrimination, are consistently significant in their impact on self-harm. Efforts to reduce these negative experiences and ensure their impact is identified and mitigated during interventions, will be key to addressing TGD self-harm.

3.5.12. Other risk factors

Race/ethnicity, income, education level, and gender identity were also examined. However, results were ambiguous. The mixed findings indicate no racial or ethnic group within the TGD community is at increased risk. Further, the heterogeneity in gender identities examined precludes further examination by gender identity. Findings also suggest income, education level, and gender identity are likely not salient risk factors for TGD self-harm or suicidality. However, because findings are mixed, we recommend researchers continue capturing these data to provide further clarity. Despite the ambiguity of findings here, clinicians should identify whether these factors are present as they may provide intervenable targets for some TGD people.

4. Discussion

This review examined and synthesised extant literature of self-harm risk and protective factors in TGD people. Clearly, TGD people experience a complex, nuanced pathway to self-harm. Three key protective (social and family support; connectedness to parents and other adults; school safety) and six risk (younger age; AFAB; depression/depressive symptoms; physical and sexual assault; drug and alcohol use; gender-minority stressors, particularly victimisation and discrimination) factors were identified. Conclusions from this review are somewhat limited due to factor heterogeneity, self-harm-related definitions, and outcome measures used. Further, replication of studies is lacking so conclusions and recommendations are made with some caution. Despite factor heterogeneity across 78 eligible studies, some crucial protective and risk factors for TGD self-harm were identified. These are important factors for clinicians to discuss with patients to create tailored, person-centred interventions [113].

4.1. Key protective factors

Protective variables presented are possible resilience factors due to their correlation with lower odds of self-harm. Social and/or family support and connectedness, especially to parents and adults, are key protective factors against TGD self-harm. This is in line with existing evidence of the protective impact of support and connectedness on TGD suicidality [28]. Family and social support may also mediate relationships between self-harm and other correlating risk factors. For example, parent connectedness has been associated with reduced substance use [62]. Therefore, encouraging and supporting TGD people to utilise existing support networks may be a key self-harm reduction strategy and reduce risky behaviours (such as substance use) associated with self-harm and wider negative health outcomes in TGD people. Additionally, family/parent counselling and support groups may foster support of TGD people, thus increasing wellbeing and addressing self-harm risk. Furthermore, TGD people lacking support (i.e., homeless; temporary housing; socially isolated; rural) need particular attention. The level and quality of existing support should be among the first factors to be established when supporting TGD people seeking help for self-harm/suicide-related behaviours. There may be differences between types of support and connectedness which should be explored in future research. For example, compared to the protective nature of parental support the impact of wider community support is less clear. This may be because negative views of TGD people differs between places or the local TGD community in included studies may be small or inaccessible which impacts how connected TGD people feel to their wider community. Understanding this will be useful to develop strategies to support TGD people and stigma-reduction programmes for the wider community.

School safety also emerged as a protective factor. These findings are supported by a recent systematic review of the role of school on LGBTQ + students' suicidal thoughts and behaviours [87]. TGD youth experience gender-identity-based hostility, victimisation, and harassment in school which cis youth do not [62]. Therefore, schools which foster a TGD-safe environment may mitigate these experiences and TGD students' self-harm risk. Creating safe spaces, being supportive of TGD students, staff/teacher training, and reducing stigma, discrimination, transphobia, and bullying in schools are strategies education settings can be implemented to engender a safe environment for their TGD students. However, findings would benefit from replication and longitudinal examination to provide a stronger evidence-base and causal effects of these protective factors. Further, these studies were all performed in the USA which may yield findings specific to the USA, or, indeed, individual US states. The presence or absence of gender-affirming school policies in other countries may yield different results and highlight the differences between different gender-affirming school policies and their impact on TGD wellbeing and self-harm.

4.2. Key risk factors

Overall, evidence from this systematic review shows younger age and people AFAB are at increased risk of self-harm/suicidality. These correlations correspond with evidence of increased risk in young people and adolescents and cis females [5] in the general population. It is interesting that increased risk is related to being AFAB, and not gender identity. Possibly, there are biological factors associated with being AFAB regardless of gender identity [26] or social learning effects relating to high rates of self-harm in people AFAB [71]. There were differences in age groups investigated. However, some studies did not specify ages, making it difficult to identify whether TGD people are at increased risk at certain ages. Future research should report age-related data in detail to evidence whether certain age-groups are at particular risk. However, the evidence presented suggests the risk for younger TGD people AFAB remains high. Drug and alcohol use is also a key factor. Substance use in TGD people is often linked to other risk factors for self-harm (i.e., victimisation [75]), so it may be a maladaptive coping mechanism employed to enable people to cope with other stressors. However, the relationship between substance use and increased self-harm and suicide outcomes is concerning. Therefore, establishing the presence of substance and alcohol use during intervention should be quickly established and may have wider benefits for TGD people.

Concerningly, TGD exposure to both physical and sexual assault are high [40], and, unsurprisingly, are key factors for TGD self-harm. TGD people face significant barriers, including further victimisation, when assaults are reported to police [90], which may further increase self-harm risk. Addressing these barriers and ensuring reported TGD assaults are taken sympathetically and seriously by police is likely to be key in reassuring TGD victims of physical and sexual assaults and may also act as a buffer against self-harm. Efforts to reduce sexual and physical assault exposure and provide resources and support are necessary to improve self-harm and wellbeing outcomes in TGD people. Also, in accord with self-harm in the general population [14], depression is a key risk factor. Depression is highly prevalent in TGD people [44,103] and often associated with other self-harm risk factors. For example, Azeem and colleagues [36] suggest the comorbidity between depression and substance (alcohol and drug) use may be due to substances being used as a maladaptive coping mechanism to combat depression and other mental health difficulties. However, while there may be temporary respite, substance use instead increases self-harm risk [36]. Consequently, substance use treatment programmes may be a good way to reduce depression and self-harm and improve wider TGD health outcomes.

Finally, gender-minority stressors (internalised transphobia, negative expectations of future events, concealment of gender identity, gender-related discrimination, rejection, victimisation, non-affirmation of gender identity) are key risk factors for self-harm in TGD people. Discrimination and victimisation are particularly important. Both are highly prevalent in TGD people [17,59], and may be linked to wider negative health outcomes [17] alongside self-harm. This is in accord with the Gender Minority Stress Model (GMS) [114] which posits the high rates of mental distress and disorders experienced by TGD people (including self-harm) relate to TGD-specific factors, such as discrimination. Consequently, TGD-specific factors may be key in understanding TGD self-harm risk [89]. Furthermore, TGD-specific factors may act as mediators between self-harm and other risk factors, such as drug and alcohol use [17]. Therefore, discrimination- and victimisation-reduction policies may be key to mitigating TGD self-harm. However, overall, studies

included in this systematic review examined general self-harm factors (e.g., depression, age). TGD people are at increased risk of self-harm and the GMS offers an explanation for this increased risk, however the current evidence-base largely focuses on general factors, not TGD-specific factors. Consequently, there is not sufficient evidence to make claims regarding the importance of TGD-specific factors to TGD self-harm. Further examination of TGD-specific factors is essential to ascertain whether TGD-specific factors explain the increased self-harm risk TGD people experience. Moreover, examining other gender-minority stressors within the GMS model (i.e., rejection, gender non-affirmation etc.) will be useful to explore the GMS model further and to establish the effects of these identity-related risk factors on TGD self-harm.

4.3. Limitations

This review identifies some important risk and protective factors for TGD self-harm which provide important intervenable targets. However, there are limitations to consider. First, that few measures are validated in TGD populations is concerning and may mean we lack a clear picture of which factors impact the self-harm pathway for TGD people. It is essential measures are developed for and validated in the populations they investigate for evaluations to be meaningful [8]. Considering this, we recommend researchers in the field commit to validating measures in TGD populations to ensure they appropriately capture TGD experiences and meaningful intervenable targets can be identified.

Second, the significant heterogeneity of factors investigated means they do not provide a robust evidence-base on which to make recommendations regarding potential intervenable targets. Further, heterogeneity meant meta-analysis of reported effect sizes was impossible. Replicating studies would further support conclusions presented here and identify the salience of other possible risk and protective factors for TGD self-harm. Additionally, TGD-specific factors are not well-researched. Therefore, the impact these have on TGD self-harm is unclear and the extant evidence is not sufficient to explain the increased self-harm risk experienced by TGD people, nor provide further support for the GMS model. We recommend research of TGD-specific self-harm factors to address this deficit in understanding.

Further, there was significant variation in self-harm-related outcome measures. This is representative of the difficulty measuring self-harm outcomes highlighted by others [115]. Moreover, the exclusion criteria and excluding grey literature possibly excluded potentially informative studies. For example, studies unavailable in English were excluded. This potentially limits the generalisability of the review findings to Western and/or English-speaking nations. Though studies from Pakistan, Lebanon, China, Hong Kong, and Dominican Republic, and others, were included and provide some generalisability. However, findings may not be generalisable to developing countries. Also, findings may not be generalisable to all TGD people as data regarding transition status and gender identity was insufficient to analyse. There may be differences between people at different stages of transition or of different gender identities. More robust evidence to clarify this may provide further opportunities for targeted support. Finally, the cross-sectional methodology employed by almost all included studies means causation cannot be determined. Future research should consider designing studies which examine causal, longitudinal, and temporal relationships between factors and self-harm outcomes. Additionally, case-control studies would provide comparisons of self-harm correlates between TGD people and the general population which would provide insight into factors distinguishing the two populations and may provide support for the GMS model and explain the disparity between self-harm risk in the general population and TGD-people.

5. Conclusion

Self-harm, and suicidal thoughts and behaviours, are common among TGD people. Investigated across 78 eligible studies, three protective and six risk factors for TGD self-harm were identified. Salient risk factors are younger age, being assigned female at birth, physical and sexual abuse, drug and alcohol use, depression or depressive symptomology, and gender-minority stressors (especially discrimination and victimisation. Protective factors are social and family support, connectedness (particularly to parents and adults), and school safety. If present, these factors provide important targets for prevention and intervention. Future research should seek to reduce heterogeneity by investigating lesser-researched factors, especially TGD-specific factors. This may identify other key factors for TGD self-harm and explore why TGD people experience increased self-harm risk The evidence here shows TGD people experience a unique, complex pathway which needs further examination to ensure intervention is appropriate and meaningful to reduce self-harm risk in this high-risk group.

Funding

KB is supported by a grant from Mental Health Research UK. ET acknowledge the support of the UK Research and Innovation (UKRI) Digital Youth Programme award (MRC project reference: MR/WOO2450/1) which was part of the AHRC/ESRC/MRC Adolescence, Mental Health and the Developing Minds programme.

PROSPERO Registration Number: CRD4023396437.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

K. Bird: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **J. Arcelus:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **L. Matsagoura:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **B.A. O'Shea:** Writing – review & editing, Writing – original draft, Supervision. **E. Townsend:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Victoria Newell for additional cross-checking in risk of bias assessment and data extraction. We would also like to thank Victoria and A. Jess Williams for useful insight which supported the analysis of the review.

Appendices.

Appendix 1 Search strategy: TGD risk and protective factors for self-harm and suicidality

("self harm*" OR "self-harm" OR "non suicidal self injur*" OR "nonsuicidal self-injur*" OR "non-suicidal self-injur*" OR NSSI OR "self injur*" OR "self-injur*" OR "self cut*" OR "self-cut*" OR "self destruct*" OR "self-destruct*" OR "deliberate self harm" OR deliberate self-harm" OR DSH OR "self-mutilat*" OR "self mutilate*" OR "self inflicted injur*" OR "self-inflicted injur*" OR overdos* OR "suicide attempt*" OR "attempted suicid*" OR parasuicide* OR *para*-suicid*" OR "para suicid*")

AND.

(transgender OR trans* OR "gender divers*" OR "non binary" OR "non-binary" OR "non-binary AND gender" OR "gender non-conforming" OR "gender non-conforming" OR "gender-queer" OR "gender queer" OR "gender fluid" OR "gender-fluid" OR "bi-gender" OR "gender creative" OR "gender neutral" OR transw* OR trans* OR "gender minorit*" OR "gender dysphoria" OR LGBT*)

Appendix 2. Gender identities under the TGD umbrella term

Gender fluid, trans, transgender, non-binary, two-spirit, omnigender, pangender, ambigender, agender, bigender, gender questioning, and gender queer. Please note this list is not exhaustive.

Appendix 3. Reasons for exclusion after full texts read

Author/s & date	Title	Reason/s for exclusion
Abramovich et al. (2020)	Assessment of Health Conditions and Health Service Use Among Transgender Patients in Canada	Did not investigate factors for self-harm (not relevant)
Albuquerque et al. (2018)	Association between violence and drug consumption with suicide in lesbians, gays, bisexuals, transvestites, and transsexuals: cross-sectional study	Data not extractable
Angoff et al. (2021)	Intersecting identities and Nonsuicidal Self-Injury Among Youth	Not relevant
Atteberry et al. (2021)	Differential Experiences of Mental Health Among Transgender and Gender-Diverse Youth in Colorado	Not relevant
Bailey et al. (2014)	Suicide risk in the UK trans population and the role of gender transition in decreasing suicidal ideation and suicide attempt	Design or analysis (qualitative analysis)
Barnett et al. (2019)	Anti-LGBT victimisation, fear of violence at school, and suicide risk among adolescents	Subpopulation not extractable (LGBT)
Beckwith et al. (2019)	Psychiatric Epidemiology of Trans & nonbinary adult patients at an urban health center	Design or analysis (suicide measured under 'psychiatrc acuity' with other mental health outcomes)
Berona et al. (2020)	Predicting suicidal behavior among lesbian, gay, bisexual, and transgender youth receiving psychiatric emergency services	Subpopulation not extractable (LGBT)
Berona et al. (2021)	Predicting the Transition From Suicidal Ideation to Suicide Attempt Among Sexual and Gender Minority Youths	Subpopulation not extractable (LGBT)
Butler et al. (2019)	Self-harm prevalence and ideation in a community sample of cis, trans and other youth	Not relevant (examined prevalence rates)
Clark et al. (2023)	The role of sleep duration in suicide risk among sexual and gender minority adolescents	Subpopulation not extractable (Sexual & Gender Minority)

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Author/s & date	Title	Reason/s for exclusion
Cramer et al. (2020)	Preferences in information processing, marginalized identity, and non-monogamy-Understanding factors in suicide-related behavior among members of the alternative sexuality community	Subpopulation not extractable
de Bolger et al. (2014)	Australian Trans Men: Developmental, Sexuality, and Mental Health	Design or analysis
Del Rio-Gonzale et al. (2021)	Sexual Orientation and Gender Identity Change Efforts and Suicide Morbidity among Gender Minority Adults in Colombia	Design (prevalence and comparison between groups)
Drakeford (2018)	Correctional Policy and Attempted Suicide Among Transgender Individuals	Examined TGD inmates
Erlangsen et al. (2023)	Transgender Identity and Suicide Attempts and Mortality in Denmark	Not relevant (examined mortality, not factors)
Freese et al. (2017)	Distinct Coping Profiles Are Associated with Mental Health Differences in Transgender and Gender Nonconforming Adults	Not relevant (Coping styles and NSSI)
Fulginiti et al. (2021)	Sexual Minority Stress, Mental Health Symptoms, and Suicidality among LGBTQ Youth Accessing Crisis Services	Subpopulation not extractable (LGBTQ)
Gibbs & Goldbach (2015)	Religious Conflict, Sexual Identity, and Suicidal Behaviors among LGBT Young Adults	Subpopulation not extractable (LGBT)
Green et al. (2021)	Association of Sexual Orientation Acceptance with Reduced Suicide Attempts among Lesbian, Gay, Bisexual, Transgender, Queer and Questioning Youth	Manuscript not available, accessible, or author/s did not respond
Gnan et al. (2019)	General and LGBTQ-specific factors associated with mental health and suicide risk among LGBTQ students	Not relevant (didn't measures factors specifically for self-harm)
Green et al. (2021)	Cumulative minority stress and suicide risk among LGBTQ Youth	Subpopulation not extractable (LGBTQ)
Hatchel et al. (2019)	Predictors of Suicidal Ideation and Attempts among LGBTQ Adolescents: The Roles of Help-Seeking Beliefs, Peer Victimisation, Depressive Symptoms, and Drug Use	Subpopulation not extractable (LGBTQ)
Hatchel et al. (2019)	Peer victimisation and suicidality among LGBTQ youth: the roles of school belonging, self-compassion, and parental support	Subpopulation not extractable (LGBTQ)
Hershner et al. (2021)	Associations Between Transgender Identity, Sleep, Mental Health and Suicidality Among a North American Cohort of College Students	Not relevant (prevalence of variables between trans and cis people, and between US and Canadian students)
House et al. (2011)	Interpersonal Trauma and Discriminatory Events as Predictors of Suicidal and Nonsuicidal Self-Injury in Gay, Lesbian, Bisexual, and Transgender Persons	Subpopulation not extractable (LGBT)
Jadva et al. (2021)	Predictors of self-harm and suicide in LGBT Youth: The role of gender, socio-economic status, bullying and school experience	Subpopulation not extractable (LGBT)
Kaniuka et al. (2019)	Stigma and suicide risk among the LGBTQ population: Are anxiety and depression to blame and can connectedness to the LGBTQ community help?	Subpopulation not extractable (LGBTQ)
Klein et al. (2023)	The Mediating Role of Family Acceptance and Conflict on Suicidality among Sexual and Gender Minority Youth	Subpopulation not extractable (LGBTQ)
Knutson et al. (2021)	Profiles of Distress and Self-Harm Among LGBTQ + Transitional Youth in a Rural State	Subpopulation not extractable (LGBTQ+)
Lee et al. (2023)	Gender Identity Change Efforts Are Associated with Depression, Panic Disorder, and Suicide Attempts in South Korean Transgender Adults	Manuscript not available, accessible, or author/s did not respond
Lee et al. (2021)	Transgender Adult's Public Bathroom-Related Stressors and their Association with Depressive Symptoms: A Nationwide Cross-Sectional Study in South Korea	Manuscript not available, accessible, or author/s did not respond
Liu et al. (2012)	Suicidal Ideation and Self-Harm in Lesbian, Gay, Bisexual, and Transgender Youth	Subpopulation not extractable (LGBT)
Lytle et al. (2018)	Suicidal and Help-Seeking Behaviors Among Youth in Online Lesbian, Gay, Bisexual, Transgender, Queer, and Questioning Social Network	Subpopulation not extractable (LGBTQQ)
McDermott et al. (2017)	The social determinants of lesbian, gay, bisexual, and transgender youth suicidality in England: a mixed methods study	Subpopulation not extractable (LGBT)
McGraw et al. (2023)	Stigma and negative mental health outcomes in sexual/gender minority youth in Utah	Subpopulation not extractable (LGBT)
McGraw et al. (2021)	Family, Faith, and Suicidal Thoughts and Behaviors (STB) Among LGBT Youth in Utah	Manuscript not available, accessible, or author/s did not respond
Mereish et al. (2014)	Interrelationships between LGBT-Based Victimisation, suicide and Substance Use Problems in a Diverse Sample of Sexual and Gender Minority Men and Women	Subpopulation not extractable (LGBT)
Moallef et al. (2022)	The relationship between sexual and gender stigma and suicide attempt and ideation among LGBTQI + populations in Thailand: findings from a national survey	Subpopulation not extractable (LGBTQI)
Morris & Galupo (2019)	"Attempting to Dull the Dysphoria": Nonsuicidal Self-Injury Among Transgender Individuals	Design (quantitative data from mixed methods is not relevant)
Patten et al. (2022)	Circumstances of Suicide Among Lesbian, Gay, Bisexual, and Transgender Individuals	Data from other sources (not individual – police, etc. after death)
Skerrett et a l. (2014)	Suicides among lesbian, gay, bisexual, and transgender populations in Australia: An analysis of the Queensland Suicide Register	Subpopulation not extractable (LGBT)
Smith et al. (2019)	Longitudinal Predictors of Self-Injurious Thoughts and Behaviors in Sexual and Gender Minority Adolescents	Subpopulation not extractable (LGBT)
Speer et al. (2022)	An Intersectional Modeling of Risk for Nonsuicidal Self-Injury Among LGBTQ Adolescents	Subpopulation not extractable (LGBT)
Spivey, L. A., & Prinstein (2019)	A Preliminary Examination of the Association between Gender Nonconformity and Suicidal Thoughts and Behaviors	Subtractable population not identifiable (not clear which results pertain to GNC youth)

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Author/s & date	Title	Reason/s for exclusion
Srivastava et al. (2021)	Differential Risks for Suicidality and Mental Health Among Transgender, Nonbinary, and Cisgender Sexual Minority Youth Accessing Crisis Services	Not relevant (No measure of risk factor/self-harm outcome significance)
Turban et al. (2021)	Timing of Social Transition for Transgender and Gender Diverse Youth, K-12 Harassment, and Adult Mental Health Outcomes	Not relevant (Measured differences between age groups of TGD people)
Ugeto et al. (2022)	Differences in suicidality and psychological symptoms between sexual and gender minority youth	Subpopulation not extractable (sexual & gender minority)
Vanbronkhorst et al. (2021)	Suicidality among Psychiatrically Hospitalized Lesbian, Gay, Bisexual, Transgender, Queer and/or Questioning Youth: Risk and Protective Factors	Manuscript not available, accessible, or author/s did not respond
Wang et al. (2021)	Methods of attempted suicide and risk factors in LGBTQ + youth	Subpopulation not extractable (LGBTQ+)
Wang et al. (2021)	Suicide attempts among Taiwanese lesbian, gay, bisexual and transgender adults during the 2018 Taiwan referendum on same-sex issues	Subpopulation not extractable (LGBT)
Watson & Tatnell (2022)	Resilience and non-suicidal self-injury in LGBTQIA+	Subpopulation not extractable (LGBTQIA+)
Watts et al. (2023)	Transgender and gender expansive emerging adults: the moderating role of thwarted belongingness on mental health	Not relevant (not measuring factors for suicide or self-harm)
White et al. (2023)	Psychological distress, self-harm and suicide attempts in gender minority compared with cisgender adolescents in the UK	Not relevant (did not measure factors against self-harm specifically)

NB: Assorted studies investigated self-harm factors in TGD military veterans or prison inmates. TGD inmates [116] and veterans [117] experience unique challenges distinguishing them from the wider TGD community which may mean they experience different self-harm pathway. Consequently, these studies were excluded. Reference lists of key primary studies and review papers were searched for relevant articles.

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The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, 1565–1579
https://doi.org/10.1210/clinem/dgad729
Advance access publication 14 December 2023
Clinical Research Article

Back to the Future: Is GnRHa Treatment in Transgender and Gender Diverse Adolescents Only an Extended Evaluation Phase?

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Abstract

Context: The role of body modifications induced by gonadal suppression in transgender and gender diverse adolescents on psychological functioning has not yet been evaluated.

Objective: The main aim of the present study was to explore several hormone, physical and psychological functioning changes during gonadotropin-releasing hormone analog (GnRHa) treatment in transgender and gender diverse adolescents (TGDAs). The potential relationship between the physical and hormone effects of GnRHa and psychological well-being, along with its magnitude, was assessed for the first time.

Methods: This prospective multidisciplinary study included 36 TGDA (22 assigned female at birth, and 14 assigned male at birth) who received psychological assessment followed by triptorelin prescription after referring to the Florence Gender Clinic. This study consisted of 3 time points: first referral (T0), psychological assessment (T1); and treatment with intramuscular injections of triptorelin for 3 up to 12 months (T2). Psychometric questionnaires were administered at each time point, and clinical and biochemical evaluations were performed at T1 and T2.

Results: The following results were found: (1) GnRHa showed efficacy in inhibiting puberty progression in TGDAs; (2) an increase in psychopathology was observed before starting GnRHa (T1) compared with baseline levels; (3) during GnRHa treatment (T2), a significant improvement in psychological functioning, as well as decrease in suicidality, body uneasiness, depression, and anxiety levels were observed; (4) hormone and physical changes (in terms of gonadotropin and sex steroid levels, height and body mass index percentiles, waist–hip ratio, and acne severity) observed during triptorelin treatment significantly correlated with a reduction in suicidal ideation, anxiety, and body image concerns.

Conclusion: Psychological improvement in TGDA on GnRHa seems to be related to the objective body changes induced by a GnRHa. Therefore, the rationale for treatment with a GnRHa may not only be considered an extension of the evaluation phase, but also the start of a medical (even if reversible) gender-affirming path, especially in TGDAs whose puberty has already progressed.

Key Words: gonadotropin-releasing hormone analog (GnRHa), gonadal suppression, transgender and gender diverse adolescents, gender incongruence, psychological functioning

Abbreviations: AFAB, assigned female at birth; ALT, alanine transaminase; AMAB, assigned male at birth; AST, aspartate transaminase; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, body mass index; BP, blood pressure; BUT, Body Uneasiness Test; EDF, effective degrees of freedom; GAGS, Global Acne Grading Scale; FG, Ferriman–Gallwey; GD, gender dysphoria; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; TGDA, transgender and gender diverse adolescent; GnRHa, gonadotropin-releasing hormone analog; MAST, Multi-Attitude Suicide Tendency Scale for Adolescents; YSR, Youth Self Report.

Transgender and gender diverse adolescents (TGDAs) may face a challenging phase of their lives at the onset or during puberty. Adolescence in transgender youth is often associated with high rates of depression, anxiety, eating disorders, suicidal thoughts and suicide attempts, and self-harming behaviors (1-7). Several reasons seem to be involved in explaining why TGDAs are a more vulnerable population than their peers. According to the minority stress model, chronic exposure to stigma and discrimination impacts strongly on psychological well-being (8, 9). In contrast, psychological functioning improves in inclusive and accepting environments after the start of specialized transgender care (10). However,

Received: 15 April 2023. **Editorial Decision:** 8 December 2023. **Corrected and Typeset:** 2 January 2024

the source of distress for some TGDAs at the onset of puberty may also be linked to pubertal body changes that are developing in an unwanted direction. International (7, 11, 12) and national (5) recommendations highlight the importance of multidisciplinary support for TGDAs seeking care. In particular, after the first phase, aimed at assessing if the pubertal body may be a source of distress according to the adolescent's gender identity and if specific criteria are met (11, 12), some TGDAs may receive a gonadotropin-releasing hormone analog (GnRHa, ie, triptorelin) to reversibly reduce gonadal steroids production and limit their possible gender-related physical effects. This step formerly known as the "extended evaluation phase" allows time to better think about further gender-affirming steps without the distress caused by unwanted pubertal body changes (13). Data about physical outcomes and the safety of GnRHa treatment in children with precocious puberty are widely available, but only a few studies have evaluated this medical therapy in TGDAs. Among the available literature in this field (14-17), several prospective studies have demonstrated the efficacy of GnRHas in terms of gonadal suppression in TGDAs, as well as their effects in terms of anthropometry and body composition (18-22). On the other hand, a study on a small sample of transgender boys reported an impact of GnRHa treatment on blood pressure, possibly leading to hypertension (23). Finally, a recent study has described a decrease in bone turnover markers in adolescents treated with GnRHa as an effect of sex steroid withdrawal (24). Follow-up studies on the use of GnRHa report an improvement in the psychological and global functioning of TGDA (25, 26). However, the role of body modifications induced by gonadal suppression on psychological functioning has not yet been evaluated. The present study aims to assess whether gender-physical and hormone modifications observed during GnRH treatment are related to changes in psychobiological functioning changes over time.

Materials and Methods

Participants

Youths referred to our Florence Gender Clinic from September 2014 to December 2020 were enrolled, provided they met the following criteria: (1) age under 18 years; (2) DSM 5 criteria for gender dysphoria (GD) (27); (3) Endocrine Society and World Professional Association for Transgender Health (WPATH) Standards of Care criteria, seventh version, for gonadotropin-releasing hormone analog (GnRHa) treatment (12, 28).

According to the existing guidelines at the time of the study (5, 12, 28), the first referral was followed by a psychological assessment, during which youths and families received support and counselling regarding the person's gender identity. When psychological criteria were met (5, 12, 28), the adolescents were referred to the endocrinologist for a GnRHa.

Study Design

This was a prospective quasi-experimental 1-group pretest–post-test study. In this design, the same group of participants is measured before (pretest) and after (post-test) a treatment or intervention is administered. Given that the group of participants who received the intervention was selected in a nonrandom way, it is considered a quasi-experimental design. The enrolled adolescents were evaluated at 3 different time points: at first referral, before receiving any kind of support for their gender identity issues (T0); after a first step of psychological assessment and just before starting the medical treatment with a GnRHa (T1); after being treated with a GnRHa for at least 3 months (T2). The maximum follow-up time was 12 months. In particular, gonadal suppression treatment consisted of the intramuscular administration of triptorelin 3.75 mg every 28 days, with interval adjustments based on clinical and laboratory data. No other gender-affirming hormonal treatments other than triptorelin (ie, no testosterone or estradiol therapy) were prescribed during the follow-up period. All participants underwent an initial period of psychological evaluation, during which criteria for GnRHas were assessed and which lasted a median of 7.0 (range 4.0-8.5) months. A further follow-up was carried out a median of 6.0 (range 6.0-12.0) months after the beginning of GnRHa. At each time point, adolescents were asked to complete several psychometric questionnaires; in addition, a medical assessment was performed at T1 and T2. It is important to remark that both an endocrinological and a psychological visit were required every 3 months as a requisite for treatment; in this regard, psychological support was part of the clinical protocol together with GnRHa. Participants and their parents gave their written informed consent for both medical treatment and participation in the study. The study design was approved by the Florence University Hospital ethics committee (2013/0016117).

A total of 154 adolescents were referred to our center from September 2014 to December 2020. Of these, 4 adolescents did not satisfy the DSM 5 criteria for GD; 14 were aged 18 by the time psychological assessment was completed and had started gender-affirming hormonal treatment, and 18 dropped out. In all, 36 adolescents were included in the final analysis; when the analysis was performed, 72 adolescents were still in the psychological assessment phase, and 10 were in the endocrinological assessment phase (for indications and contraindications for treatment). The slight overrecruitment compared with the initial power calculation was due to the need to compensate for the possibility of drop-outs. Given that, in the end, more participants completed the study approximately within the same time frame, 2 additional subjects were included beyond what was initially anticipated. Participants who dropped out had baseline psychometric characteristics similar to those who were included in the final analyses (see Table 1). Figure 1 reports the details of the participants in a flow chart.

In relation to the novel objective of this study, which was to investigate the relationship between physical and hormone changes induced by GnRHa treatment and psychometric measures, based on similar regression models concerning body uneasiness, carried out on an adult population of subjects with GD treated with hormonal therapy, medium effect sizes of $\beta = .45$ were hypothesized a priori, corresponding to an f^2 of approximately 0.25 (29). Power analysis for a linear regression model with $\alpha = .05$ indicates that a sample of at least 34 individuals is sufficient to identify a statistically significant effect size of this magnitude with a power of 0.80. Accordingly, the sample recruited for this study was considered adequate. The study was considered complete with the execution of the last planned follow-up, once the calculated sample size was reached.

Sociodemographic and Psychometric Evaluations

TGDAs and their parents completed a structured interview to collect sociodemographic characteristics at the time of the first

Table 1. Comparisons between participants who dropped out and those who completed the study and were included in the final analyses, performed using analysis of covariance (with age and Tanner stage as covariates)

	Dropouts (n = 18)	Treatment completers (n = 36)	F	*P*
YSR Total Score	65.50 ± 6.72	62.94 ± 10.07	0.29	.593
YSR Externalizing	56.00 ± 5.39	55.75 ± 8.91	0.03	.863
YSR Internalizing	68.00 ± 8.54	67.33 ± 11.61	0.01	.921
YSR Aggressive Behavior	54.83 ± 3.31	57.75 ± 6.52	0.92	.342
YSR Rule-Breaking Behavior	55.11 ± 4.34	55.84 ± 6.26	0.48	.492
YSR Attention Problems	62.11 ± 9.16	62.44 ± 9.26	0.04	.842
YSR Thought Problems	61.00 ± 8.19	61.28 ± 11.67	0.04	.842
YSR Social Problems	63.33 ± 4.92	62.59 ± 9.02	0.02	.888
YSR Somatic Complaints	63.33 ± 10.58	66.38 ± 12.18	0.41	.523
YSR Withdrawn/Depressed	65.44 ± 7.02	66.75 ± 13.13	0.15	.700
YSR Anxious/Depressed	67.56 ± 10.26	66.31 ± 10.97	0.07	.792
MAST Attraction to Death	2.60 ± 0.98	2.67 ± 1.24	0.07	.792
MAST Repulsion by Life	2.98 ± 0.69	2.88 ± 0.67	0.04	.842
MAST Attraction to Life	2.90 ± 0.52	3.49 ± 1.10	1.33	.254
MAST Repulsion by Death	2.54 ± 1.72	2.52 ± 1.56	0.01	.921
BUT-A GSI	3.03 ± 1.00	2.98 ± 0.90	0.01	.921
BDI	22.67 ± 14.83	17.52 ± 11.52	0.73	.397
BAI	24.44 ± 14.65	18.13 ± 10.93	0.74	.394

No comparison was statistically significant (all $P > .05$).
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BUT, Body Uneasiness Test; MAST, Multi-Attitude Suicide Tendency Scale; YSR, Youth Self Report.

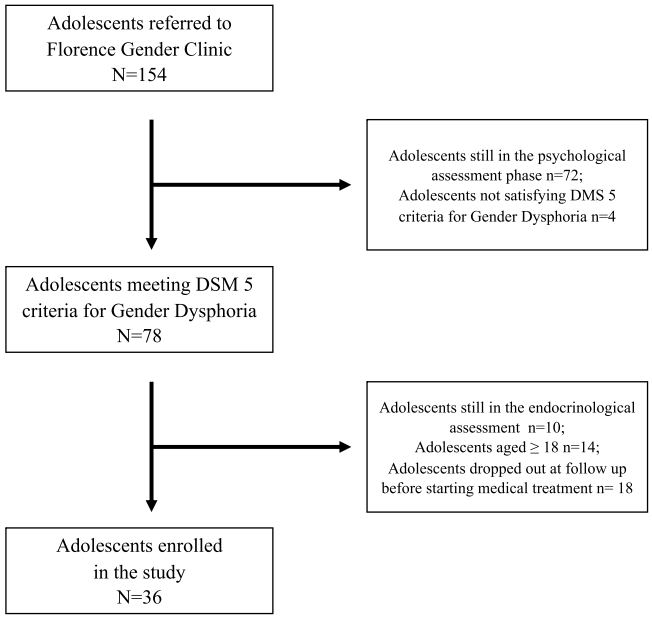

Figure 1. Flow chart reporting details of the participants.

referral. At the same time, TGDAs were asked to complete several psychometric questionnaires, including the Youth Self Report (YSR) (30, 31), the Body Uneasiness Test (BUT) (32, 33), the Multi-Attitude Suicide Tendency Scale for Adolescents (MAST) (34, 35), the Beck Depression Inventory (BDI)-II (36), and the Beck Anxiety Inventory (BAI) (37).

A description of the aforementioned questionnaires is reported in Table 2.

Physical Assessment and Laboratory Measurements

Adolescents on GnRHas attended an endocrinological visit every 3 months; the visit included a physical examination for systolic and diastolic blood pressure (BP) (mean of 3 measurements 5 minutes apart, in a sitting position, with a standard sphygmomanometer), height, weight, waist circumference, hip circumference, body and face hair distribution using the Ferriman–Gallwey score (FG score) (38), acne severity using the Global Acne Grading Scale (GAGS) (39), and Tanner stage. Tanner stage evaluation was based on breast growth in assigned female at birth (AFAB) adolescents and on genital development and testicular volume in assigned male at birth (AMAB) adolescents (40). Height was measured using a wall-mounted stadiometer and weight with a digital floor scale. Height and weight were used to calculate body mass index (BMI; kg/m^2). The mean BP was calculated as (diastolic BP + (1/3×difference between systolic and diastolic BP) (41).

Blood tests were performed at least 3 weeks before each consultation, and laboratory measurements included gonadotropins, sex steroids, liver function parameters, fasting glucose, glycated hemoglobin (HbA1c), lipid profile test; a biochemical assessment was performed in the morning, in fasting conditions, to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), 17β-estradiol (using the chemiluminescence method; DIMENSION VISTA System, Siemens), testosterone (by liquid chromatography mass spectrometry; Agilent Technologies, Santa Clara, CA), HbA1c, glucose, liver enzymes aspartate transaminase (AST), alanine transaminase (ALT), cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

Table 2. Descriptions of questionnaires used in the study

Youth Self Report
The Youth Self Report (YSR) is a self-rating scale evaluating emotional and behavioral functioning of adolescents through a 3-point scale (from 0 = not true to 2 = very true). It consists of about 100 items grouped in 8 syndrome scales according to a dimensional approach (anxiety and depression, withdrawal and depression, somatic complaints, social problems, problems of thought, problems of attention, rule transgression behavior, aggressive behavior) ,and 3 general scales (total problem, internalizing, and externalizing scale). Raw scores are transformed into T scores based on normative data in relation to norms for their age and gender.
Body Uneasiness Test
The Body Uneasiness Test (BUT) is a self-rating scale evaluating different areas of body-related psychopathology, such as weight phobia, avoidance, compulsive control behavior, experiencing separation and strangeness from the body, and specific worries about certain body parts or characteristics. Subjects rate 34 different body image experiences (BUT A), reporting how often they happen to dislike each experience. Higher scores indicate greater body uneasiness.
Multi-Attitude Suicide Tendency Scale for adolescents
The Multi-Attitude Suicide Tendency Scale for adolescents (MAST) is a self-rating scale evaluating suicidal tendency which reflect 4 types of attitudes: attraction to life, attraction to death, repulsion by life and repulsion by death. In particular, the "repulsion by life" component reflects such experiences as stress and pain; "attraction to death" represents religious convictions or perceptions that death is a superior way of being; "attraction to life" is based on the level of satisfaction with life and a sense of well-being; and "repulsion by death" indicates fears of death. Each item is rated on a 5-point scale (from 1 = strongly agree to 5 = strongly disagree).
Beck Depression Inventory
The Beck Depression Inventory (BDI-II) is a self-rating scale that measures depressive symptoms in emotional, cognitive, and somatic dimensions. Each item is rated on a 4-point Likert scale (from 0 to 3), taking into consideration the past 2 weeks as time frame. Higher scores indicate greater levels of depressive symptoms. Scores may range from 0 to 63 with the following cut offs: 0-13 = minimal depression; 14-19 = mild depression; 20-28 = moderate depression and 29-63 = severe depression.
Beck Anxiety Inventory
The Beck Anxiety Inventory (BAI) is a self-rating scale evaluating the intensity of physical and cognitive anxiety symptoms considering the past week as time frame. It consists of 21 items rated on a 4-point Likert scale (from 0 = not at all to 3 = severely). Higher scores indicate greater levels of anxiety. Scores may range from 0 to 63 with the following cut offs: 0-7 = minimal anxiety; 8-15: mild anxiety; 16-25: moderate anxiety and 26-63: severe anxiety.

(HDL-C), and triglycerides (by routine clinical chemistry methods). To estimate LDL-C the Friedewald equation was used: LDL-C = total cholesterol − (HDL cholesterol + triglycerides/5) (42). All the above-mentioned psychological, biochemical, and physical assessment tools were part of the standard clinical protocol applied to all youths referred to the gender clinic.

Statistical Analysis

Tanner stage was reported using the median and interquartile range (IQR). Continuous data were reported as mean and SD, with the exception of endocrinological characteristics expected to be near 0 in at least 1 group at at least 1 time point (gonadotropins, sex steroid), or parameters with a skewed evaluation and hence possibly 0 inflated (like GAGS and FG scores), which were reported using median and IQR. The comparisons of psychometric variables between participants who completed the treatment and those who dropped out were conducted using analysis of covariance, with age and Tanner stage as covariates. The F values were reported, corresponding to the ratio of the variance between groups to the variance within groups (larger F values indicates that the between-group variation is larger than the within-group variation), along with their corresponding *P* values.

Regarding longitudinal analyses, 3 different approaches were adopted. Tanner stage evolution over time before and after GnRHa therapy was investigated with the Wilcoxon signed rank test, a nonparametric paired-samples test for ordered variables. Regarding laboratory measurements, a nonlinear variation was expected over time after administration of the GnRHa, and preliminary analyses confirmed this hypothesis. Therefore, generalized additive mixed models with random intercepts were used in order to capture nonlinear trends in the longitudinal context. In all generalized additive mixed models, time was entered as a smooth term based on thin plate regression splines, which are considered optimal (43); a modified smoothing penalty was used in order to allow the smooth term to be shrunk to 0 and avoid overfitting (43). The models for FSH and LH were adjusted for Tanner stage, while those for waist and hip circumferences were adjusted for BMI. Moreover, assigned sex at birth was entered as a fixed effect, with individual time smooth terms computed for each group to differentiate between AMAB and AFAB. In accordance with common guidelines for statistical reporting, the F value and its corresponding *P* value, as well as effective degrees of freedom (EDF), have been provided for all smooth terms. In this context, EDF can be used as a proxy for measuring the nonlinearity of the relationship between the variables in the model: a value less than or equal to 1 indicates a substantial linear trend of the dependent variable over time, while a value greater than 1 indicates an increasingly curved longitudinal trend. For significant time smooth terms, the first derivatives of the fitted trend and their respective 95% CI were computed using standard theory: a time interval where the CI on the first derivative did not include 0 was considered to be a period of statistically significant change (44). Finally, linear mixed models with random intercepts (with Tanner stage and age as covariates) were used to investigate the longitudinal trend of all psychometric measurements, given that they did not show nonlinear trends in preliminary analyses. The time variable was entered into the model as a 3-level polytomous independent variable, where each patient's longest follow-up was considered for the GnRHa treatment period. F tests for the fixed effect time were reported for each model. For every statistically significant F test, which indicates at least 1 variation over time different from 0, was identified; post hoc pairwise tests were performed to identify the periods of change.

To test the additional effect of GnRHa administration on psychometric variables compared with psychological support alone, moderation models were also performed in which time, the presence of GnRHa (before GnRHa vs after GnRHa) and their interaction were included as predictors; a statistically significant time × GnRHa interaction indicated a different longitudinal trend between the 2 periods and was consequently probed using simple effects analysis.

Finally, linear regression analyses were used to test whether physical or endocrinological changes over time predicted variations in psychometric scores, adjusting for Tanner stage and

Table 3. Physical and endocrinological characteristics of the sample before (T1) and after (T2) the beginning of GnRHa, divided by assigned sex at birth

	AMAB (n = 14)		AFAB (n = 22)	
	Before GnRHa (T1)	After GnRHa (T2)	Before GnRHa (T1)	After GnRHa (T2)
SBP (mmHg)	114 ± 11	114 ± 9	111 ± 10	110 ± 10
SPB percentile	55.4 ± 26.4	53.1 ± 26.0	51.3 ± 27.7	46.14 ± 28.4
DBP (mmHg)	70 ± 7	74 ± 7	71 ± 7	70 ± 9
DBP percentile	65.1 ± 23.1	74.4 ± 22.4	64.8 ± 19.6	63.2 ± 24.9
Mean BP (mmHg)	85 ± 8	87 ± 6	84 ± 8	84 ± 9
Weight (kg)	58.9 ± 12.4	60.6 ± 11.4	63.5 ± 17.5	67.2 ± 16.2
Height (cm)	167.3 ± 9.4	169.3 ± 8.3	161.9 ± 5.6	162.8 ± 5.1
Height percentile	63.9 ± 34.4	56.2 ± 35.1	58.0 ± 26.4	58.9 ± 26.1
BMI percentile	62.2 ± 39.0	63.9 ± 27.3	69.8 ± 29.5	78.1 ± 22.4
Waist (cm)	79.0 ± 8.9	76.9 ± 8.0	85.6 ± 14.2	87.4 ± 14.2
Hip (cm)	91.5 ± 6.8	92.0 ± 6.6	98.0 ± 13.6	101.5 ± 12.1
Ferriman–Gallwey (FG) score	8.0 (6.3-13.3)	4.5 (3.0-7.5)	6.0 (2.3-8.8)	3.50 (2.3-6.8)
Global Acne Grading System (GAGS)	7.5 (0.0-16.8)	0.0 (0.0-7.3)	8.0 (0.3-21.5)	4.5 (0.0-9.5)
LH (mUI/mL)	3.1 (2.3-4.0)	0.8 (0.3-1.2)	4.6 (3.6-6.2)	0.5 (0.3-1.0)
FSH (mUI/mL)	4.9 (4.1-5.9)	0.6 (0.3-1.0)	4.4 (3.1-5.1)	2.8 (1.8-3.4)
Testosterone (nmol/L)	18.4 (15.6-21.0)	1.0 (0.4-2.9)	1.2 (0.8-1.8)	0.7 (0.7-1.1)
Estradiol (pmol/L)	77.2 (59.6-110.2)	36.8 (15.0-70.0)	114.0 (70.0-228.4)	18.4 (15.0-36.8)
HbA1C (mmol/mol)	33.1 ± 3.8	34.7 ± 4.0	33.6 ± 8.2	34.2 ± 6.7
AST (UI/L)	20.3 ± 6.6	20.4 ± 7.5	17.5 ± 4.1	23.6 ± 11.1
ALT (UI/L)	19.9 ± 11.7	17.4 ± 6.7	14.9 ± 6.5	19.4 ± 8.1
Total cholesterol (mg/dL)	152.0 ± 24.0	158.4 ± 30.2	155.3 ± 22.7	165.3 ± 26.4
Triglycerides (mg/dL)	60.2 ± 23.4	66.6 ± 32.6	76.0 ± 26.8	80.4 ± 39.2
HDL cholesterol (md/dL)	56.6 ± 14.4	63.5 ± 13.0	54.6 ± 9.3	55.6 ± 9.0
LDL cholesterol (mg/dL)	79.1 ± 14.9	76.3 ± 24.3	86.7 ± 17.1	93.8 ± 24.5

Between-group comparisons were not performed as they were considered irrelevant to the objectives of the study.
Abbreviations: AFAB, assigned female at birth; ALT, alanine transaminase; AMAB, assigned male at birth; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; TGNA, transgender and gender nonconforming adolescents.

taking into account the moderating role of sex assigned at birth. Among the available laboratory variables, LH and FSH were included in these analyses (considered the main outcomes of the effectiveness of GnRHa treatment), while among the physical variables, only those that were estimated to have a significant impact on psychological well-being were considered: height, weight, BMI, waist/hip circumference, and FG and GAGS scores. As for the psychometric variables, to limit the number of associations to be tested, the MAST ideation scores and the measures of body uneasiness (BUT-A GSI), depression (BDI), and anxiety (BAI) were included.

Data were analyzed using R Statistical Software v. 4.1.2 (45) and the following packages: ggplot2, gratia, mgcv, nlme, reghelper, sjPlot (43, 46-50).

Results

A total of 36 adolescents were enrolled in this study, of which 14 were AMAB and 22 were AFAB, with an average age of 14.19 ± 1.88 years; the age range was 11-15 years old and 9-17 years old for AMAB and AFAB adolescents, respectively. Tanner stage ranged from 3 to 5, with a median of 5 (IQR 4-5).

Endocrinological Evaluation

All endocrinological characteristics of the sample are reported in Table 3, before and after GnRHa therapy.

After GnRH therapy, a total of 9 patients (25.0%) reported a reduction in Tanner stage at the final evaluation. This transition towards lower Tanner stages was statistically significant, as evidenced by the Wilcoxon signed rank test ($P = .005$); Fig. 2 shows the violin plots at the 2 time points. In all the AFAB adolescents who had menarche (n = 20, 90.01%), menses stopped at T3. Nonlinear longitudinal analyses are reported in Table 4. On average, participants of both groups grew taller, whereas a significant increase in total weight was observed only in the AFAB group (Table 4 and Fig. 3A and 3B, respectively). These changes were basically linear, as indicated by the EDFs, which were close to 1 (Table 4), and the analyses of the first derivatives of the fitted splines confirmed that they were significantly different from 0 over the entire follow-up period (Fig. 3A and 3B). AMAB individuals experienced a progressive reduction in height percentiles (Table 4 and Fig. 3C), whereas a significant increase in BMI percentiles was observed in AFAB individuals, but only from the third month of therapy and only for a few months (Table 4 and Fig. 3D). Both hair growth and acne

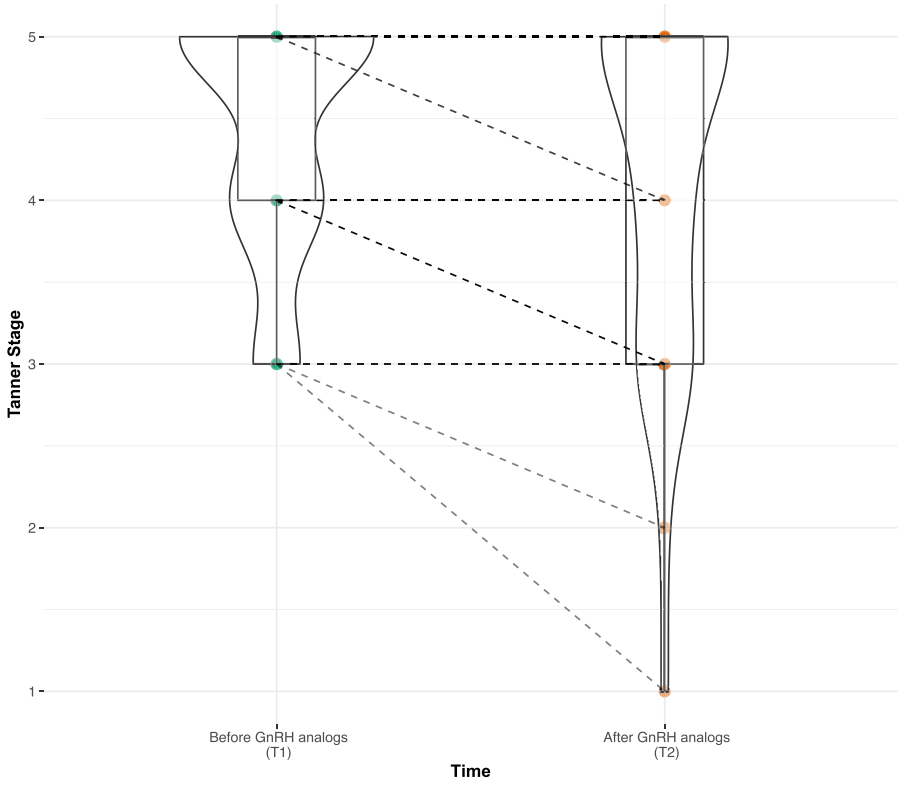

Figure 2. Violin plot of Tanner stages before (T1) and after (T2) the beginning of GnRHa treatment. Each "violin" in the plot corresponds to a specific time point, with its width indicating the frequency of Tanner stages at that time. The wider sections of the violin plot represent a higher density of data points. The individual points within each violin represent the actual data for the Tanner Stage at each time point. The lines connecting the points illustrate the progression of Tanner stages over time. The rectangles within each violin represent the interquartile range of the data.

severity were significantly reduced in all participants after initiation of GnRHa, especially in AMAB individuals (Table 4 and Fig. 3E and 3F).

The data analyses confirmed a general reduction in levels of gonadotropins; in particular, FSH levels decreased nonlinearly and faster over the first months of GnRHa treatment in AMAB individuals, while the same trend was observed for LH in AFABs (Table 4 and Fig. 3G and 3H). In the AMAB group alone, testosterone levels fell in the first half of the observation period under GnRHa, and then stabilized in the second half at levels similar to those in the AFAB group (Table 4 and Fig. 3I). Estradiol levels decreased significantly and approximately linearly in AFAB individuals during the first 10 months of GnRHa treatment (Table 4 and Fig. 3I). No statistically significant changes were observed in either AMAB or AFAB with regards to BP, waist and hip circumferences, HbA1c, AST, ALT, and lipid levels, with the exception of a slight elevation of HDLs in AMAB individuals (Table 4 and Fig. 3K).

Psychometric Evaluation

All psychometric characteristics of the sample at all time points are reported in Table 5. Longitudinal analyses are reported in Table 6. After GnRHa therapy, a significant reduction in both externalizing and internalizing problems was observed (Table 6). In particular, participants reported lower scores on scales related to thought and social problems, somatic complaints, and anxious–depressive symptomatology (Table 6). Almost every improvement was observed after initiation of GnRHa therapy, with the exception of YSR Withdrawn/Depressed (Table 6). Conversely, the overall YSR score significantly worsened during the initial assessment follow-up period, whereas an amelioration was observed after GnRHa therapy (Table 6). A similar trend was observed for body uneasiness and repulsion by life which, after an initial (although not statistically significant) slight increase, significantly improved after GnRHa therapy compared with the previous follow-up (Table 6). Figure 4 shows the longitudinal trends of YSR total score, BDI, BAI, MAST Repulsion by Life, and BUT-A GSI.

In order to confirm that GnRHa therapy had a different effect on psychopathological domains than psychological assessment alone, moderation analyses were performed taking into account the duration of treatment, while adjusting for age and Tanner stage. As indicated by the statistically significant interaction effect ($b_{Time*GnRHa} = -1.08$, $P < .001$), the longitudinal course of YSR total score exhibited an inverted tendency over time following GnRHa treatment (indicating a moderating effect), with adolescents experiencing an increase in psychopathology before ($b_{Before\ GnRHa} = 0.54$, $P = .006$) and a progressive amelioration after initiation of therapy ($b_{After\ GnRHa} = -0.54$, $P = .015$). A similar trend was observed on MAST Repulsion by Life ($b_{Time*GnRHa} = -0.08$, $P = .028$; $b_{Before\ GnRHa} = 0.01$, $P = .675$; $b_{After\ GnRHa} = -0.07$, $P = .010$), body uneasiness ($b_{Time*GnRHa} = -0.07$, $P = .001$; $b_{Before\ GnRHa} = 0.01$, $P = .468$; $b_{After\ GnRHa} = -0.06$, $P < .001$), and BAI scores ($b_{Time*GnRHa} = -0.61$, $P = .049$; $b_{Before\ GnRHa} = -0.15$, $P = .449$; $b_{After\ GnRHa} = -0.76$, $P = .001$). These moderation effects are shown in Fig. 5.

Correlations between endocrinological and psychometric modifications

The total reduction in LH levels observed at follow-up after GnRHa therapy was significantly associated with the

Table 4. Longitudinal analysis of physical and endocrinological measurements

		AMAB TGDA			AFAB TGDA		
	Group fixed effect (AFAB vs AMAB TGDA)	EDF	F (smooth term)	Period of significant change (months)	EDF	F (smooth term)	Period of significant change (months)
SBP (mmHg)	−3.61, $P = .205$	0.00	0.00, $P = .531$	—	0.00	0.00, $P = .381$	—
SPB percentile	−5.62, $P = .465$	0.00	0.00, $P = .503$	—	0.26	0.12, $P = .262$	—
DBP (mmHg)	−1.37, $P = .558$	0.76	0.98, $P = .058$	—	0.61	0.48, $P = .138$	—
DBP percentile	−5.63, $P = .411$	0.70	0.73, $P = .087$	—	0.44	0.25, $P = .204$	—
Mean BP (mmHg)	−2.16, $P = .352$	0.07	0.03, $P = .316$	—	0.50	0.32, $P = .181$	—
Weight (kg)	5.77, $P = .262$	0.50	0.32, $P = .177$	—	1.03	**5.95, $P < .001$**	0.00-12.00
Height (cm)	**−5.86, $P = .014$**	1.10	**10.60, $P < .001$**	0.00-12.00	0.95	**3.15, $P = .002$**	0.00-12.00
Height percentile	−1.79, $P = .858$	1.04	**5.89, $P < .001$**	0.00-11.46	0.00	0.00, $P = .682$	—
BMI percentile	11.09, $P = .193$	0.00	0.00, $P = .917$	—	0.85	**1.53, $P = .025$**	2.99-8.43
Waist (cm)	0.72, $P = .696$	0.74	0.92, $P = .068$	—	0.00	0.00, $P = .427$	—
Hip (cm)	1.02, $P = .554$	0.00	0.00, $P = .872$	—	0.42	0.24, $P = .212$	—
Ferriman Gallwey (FG) score	−2.76, $P = .160$	1.04	**6.83, $P < .001$**	0.00-12.00	0.85	**1.61, $P = .022$**	1.53-7.54
Global Acne Grading System (GAGS)	1.91, $P = .510$	0.97	**3.61, $P = .001$**	0.00-12.00	0.90	**2.15, $P = .010$**	0.00-9.45
LH (mUI/mL)	0.56, $P = .506$	0.99	**3.34, $P = .004$**	0.00-10.21	1.86	**18.80, $P < .001$**	0.00-6.51
FSH (mUI/mL)	0.77, $P = .383$	1.99	**12.45, $P < .001$**	0.00-4.98	0.93	**2.18, $P = .016$**	0.00-7.82
Testosterone (nmol/L)	**−9.28, $P < .001$**	2.36	**85.20, $P < .001$**	0.00-6.63	0.00	0.00, $P = .626$	—
Estradiol (pmol/L)	39.30, $P = .301$	0.00	0.00, $P = .435$	—	0.98	**3.02, $P = .003$**	0.00-9.93
HbA1C (mmol/mol)	0.01, $P = .997$	0.68	0.68, $P = .094$	—	0.00	0.00, $P = .738$	—
AST (UI/L)	−0.02, $P = .995$	0.00	0.00, $P = .662$	—	0.76	0.83, $P = .082$	—
ALT (UI/L)	−1.72, $P = .499$	0.00	0.00, $P = .361$	—	0.05	0.02, $P = .325$	—
Total cholesterol (mg/dL)	5.19, $P = .524$	0.76	0.99, $P = .059$	—	0.66	0.60, $P = .115$	—
Triglycerides (mg/dL)	13.80, $P = .138$	0.00	0.00, $P = .331$	—	0.00	0.00, $P = .722$	—
HDL cholesterol (md/dL)	−4.10, $P = .230$	0.96	**3.37, $P = .002$**	0.00-12.00	0.00	0.00, $P = .781$	—
LDL cholesterol (mg/dL)	12.21, $P = .077$	0.00	0.00, $P = .975$	—	0.74	0.85, $P = .075$	—

Group fixed effects represent the average difference in the outcome variable associated with being a member of the AFAB group compared with the AMAB group, across all time points. Nonlinear time effects are reported as F values (for the smooth terms) with their respective effective degrees of freedom (EDF) and *P* values. EDF can be used as a proxy for measuring the nonlinearity of the relationship between the variables in the model: a value less than or equal to 1 indicates a substantial linear trend of the dependent variable over time, while a value greater than 1 indicates an increasingly curved longitudinal trend. For significant effects, the period of significant change is also reported. Bold values denote statistical significance at the $P < .05$ level.
Abbreviations: AFAB, assigned female at birth; ALT, glutamic-pyruvic transaminase; AMAB, assigned male at birth; AST, glutamic-oxaloacetic transaminase; BMI body mass index; DBP, diastolic blood pressure, HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; TGDA, transgender and gender diverse adolescents.

reduction in suicide ideation as measured by the MAST Repulsion by Life subscale, but only in AMAB individuals ($b_{\Delta LH*Group} = -0.96$, $P < .001$; $b_{AMAB} = 0.93$, $P < .001$; $b_{AFAB} = -0.03$, $P = .727$) (Fig. 6A). The same effects on suicide ideation were observed for the reduction in FSH levels ($b_{\Delta FSH*Group} = -0.65$, $P = .001$; $b_{AMAB} = 0.53$, $P < .001$; $b_{AFAB} = -0.13$, $P = .316$) (Fig. 6B). Similarly, the reduction in body uneasiness was associated with that of LH levels in AMAB individuals ($b_{\Delta LH*Group} = -0.40$, $P = .006$; $b_{AMAB} = 0.28$, $P = .025$; $b_{AFAB} = -0.13$, $P = .078$) (Fig. 6C) and of FSH levels in all adolescents ($b_{\Delta FSH} = 0.19$, $P = .031$; $b_{\Delta FSH*Group} = -0.05$, $P = .635$) (Fig. 6D). Additionally, lower FSH levels after GnRHa correlated with lower anxiety levels, with no significant differences between AMAB and AFAB adolescents ($b_{\Delta FSH} = 2.56$, $P = .030$; $b_{\Delta FSH*Group} = -1.86$, $P = .218$) (Fig. 6E).

Considering the relationship between physical changes and psychopathology, the reduction in waist circumference was associated with a reduction in suicidal risk in AMAB individuals in terms of attraction to death ($b_{\Delta Waist*Group} = -0.11$, $P = .015$; $b_{AMAB} = 0.09$, $P = .015$; $b_{AFAB} = -0.03$, $P = .322$) and repulsion by life ($b_{\Delta Waist*Group} = -0.23$, $P = .030$; $b_{AMAB} = 0.24$, $P = .005$; $b_{AFAB} = 0.01$, $P = .957$). Similarly, in the same group, the reduction in the waist–hip ratio correlated with the reduction in repulsion by life ($b_{\Delta Waist/Hip*Group} = -24.86$, $P = .017$; $b_{AMAB} = 21.68$, $P = .009$; $b_{AFAB} = -3.18$, $P = .588$) and anxiety levels ($b_{\Delta Waist/Hip*Group} = -210.43$, $P = .004$; $b_{AMAB} = 121.99$, $P = .025$), whereas in AFAB individuals a reduced waist–hip ratio resulted in higher anxiety ($b_{AFAB} = -88.44$, $P = .035$) (Fig. 6F). Improved acne severity was associated with reduced suicidal risk (MAST Repulsion by Life) in both groups ($b_{\Delta GAGS} = 0.15$, $P = .18$; $b_{\Delta GAGS*Group} = -0.09$, $P = .260$). Finally, in AMAB individuals lower body uneasiness levels were associated with reductions in weight ($b_{\Delta Weight*Group} = -0.21$, $P = .007$; $b_{AMAB} = 0.15$, $P = .011$; $b_{AFAB} = -0.06$, $P = .145$) and BMI percentile

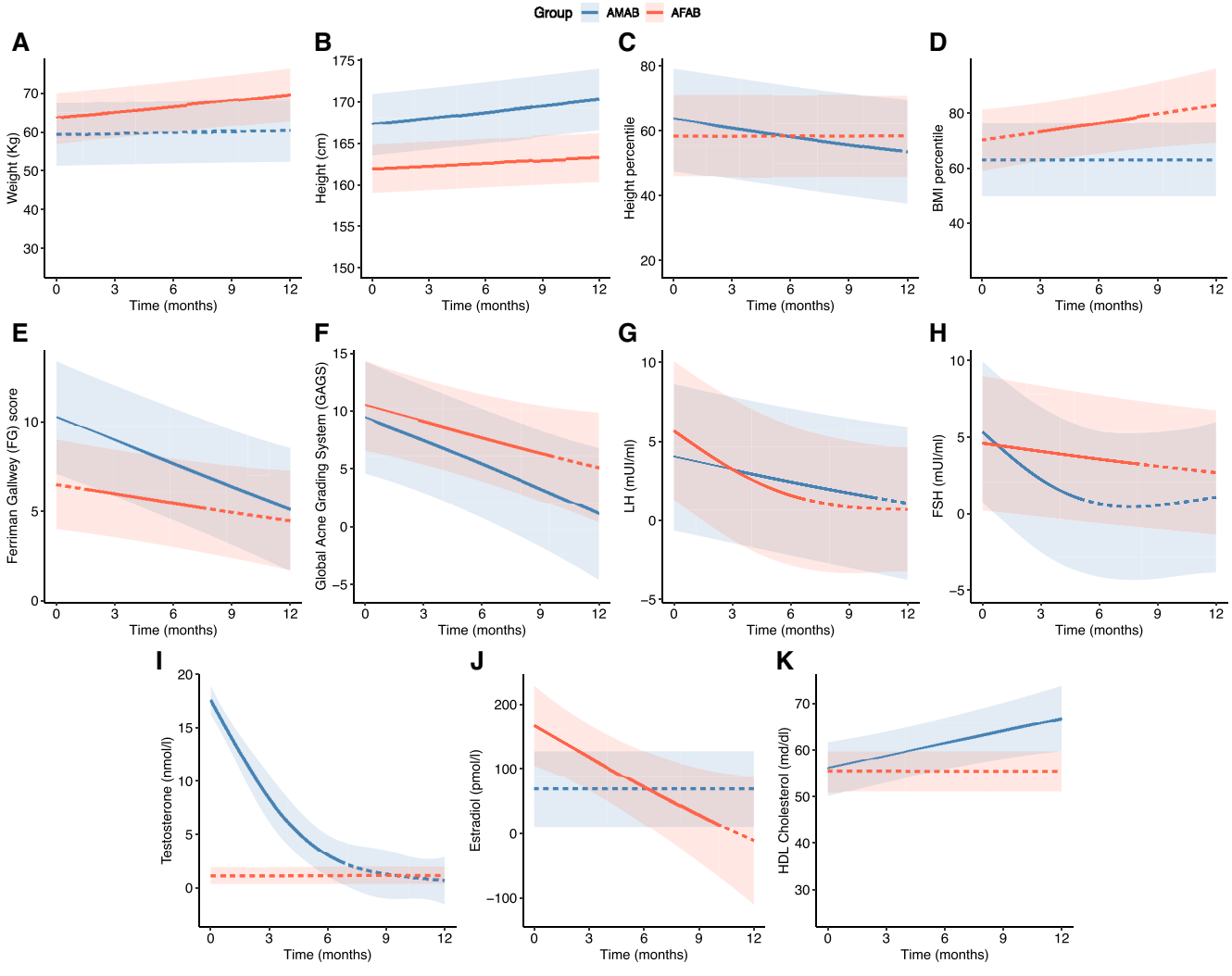

Figure 3. Physical and endocrinological characteristics over time after the beginning of GnRHa treatment. The lines represent generalized additive mixed model-based predicted values, whereas ribbons illustrate the range corresponding to 2 standard errors from such values. To allow for the complete depiction of the ribbons, the Y-axis has been permitted to extend below 0.

($b_{\Delta BMIperc*Group} = -0.03$, $P = .041$; $b_{AMAB} = 0.02$, $P = .024$; $b_{AFAB} = -0.01$, $P = .460$), whereas all adolescents reported greater body uneasiness with decreasing percentile height ($b_{\Delta HeightPerc} = -0.05$, $P = .031$; $b_{\Delta HeightPerc*Group} = 0.01$, $P = .956$).

Discussion

This is the first follow-up study exploring the impact of the possible correlation between GnRHa-induced physical or hormone changes and psychological well-being in TGDAs. The strength of the present study is in its multidisciplinary prospective design, which evaluates both the psychological and endocrinological aspects of GnRHa treatment. The size of the relationship between psychological and endocrinological effects of this treatment is also assessed. Furthermore, the psychobiological changes associated with GnRHa treatment have been systematically evaluated for the first time in a sample of Italian TGDAs. The main results of the present study were as follows: (1) GnRHa treatment was followed by a significant inhibition of puberty progression in TGDAs; (2) during GnRHa treatment, a significant improvement in psychological functioning as well as a decrease in suicidal ideation and body uneasiness, and depression and anxiety levels were observed; (3) a significant improvement in psychopathological domains was observed during GnRHa treatment (T2), while an increase in psychopathology was observed before starting GnRHa treatment (T1) compared with baseline levels; (4) physical and hormone changes observed during triptorelin treatment showed a correlation with changes in psychological functioning, suicidal risk, anxiety, and body image concerns.

Medical Efficacy of GnRHa

As expected, significant inhibition of the hypothalamus–pituitary–gonadal axis was observed after the start of GnRHa treatment, as confirmed by endocrinological assessments. Furthermore, we here report reductions in levels of gonadotropins and sex hormones. This is clinically transduced in a partial regression of the Tanner stage, as well as in a reduction of body hair growth and of the severity of acne in both TGDAs. To the best of our knowledge, no previous studies have assessed the effects of GnRHa treatment on dermatologic outcomes in TGDAs. On average, subjects of both groups, reported a statural increase. However, a reduction in height growth was observed in AMAB adolescents according to

Table 5. Psychological characteristics of the sample at baseline (T0), before (T1) and after (T2) the beginning of GnRHa, divided by assigned sex at birth

	AMAB (n = 14)			AFAB (n = 22)		
	Baseline (T0)	After psych. assessment, before GnRHa (T1)	After GnRHa (T2)	Baseline (T0)	After psych. assessment, before GnRHa (T1)	After GnRHa (T2)
YSR Total Score	63.08 ± 9.73	71.00 ± 9.48	63.15 ± 11.14	62.84 ± 10.55	71.72 ± 14.48	66.83 ± 14.92
YSR Externalizing	52.62 ± 9.38	53.50 ± 8.54	49.57 ± 10.57	57.89 ± 8.14	57.07 ± 13.69	53.00 ± 11.39
YSR Internalizing	65.62 ± 10.98	68.75 ± 9.66	59.08 ± 8.11	68.45 ± 12.14	65.50 ± 10.82	59.00 ± 11.08
YSR Aggressive Behavior	57.58 ± 7.96	57.25 ± 6.62	55.75 ± 5.67	57.85 ± 5.71	57.73 ± 6.83	54.87 ± 7.09
YSR Rule-Breaking Behavior	52.92 ± 3.94	53.33 ± 5.26	52.00 ± 3.13	57.68 ± 6.82	60.47 ± 8.55	56.40 ± 6.42
YSR Attention Problems	62.67 ± 5.65	60.67 ± 9.59	58.10 ± 10.51	62.30 ± 11.02	63.80 ± 13.13	59.40 ± 12.02
YSR Thought Problems	57.42 ± 7.55	59.25 ± 10.55	54.33 ± 5.90	63.60 ± 13.20	61.33 ± 10.39	54.93 ± 7.60
YSR Social Problems	61.83 ± 9.00	63.92 ± 10.40	55.92 ± 6.01	63.05 ± 9.24	61.00 ± 10.73	57.29 ± 10.34
YSR Somatic Complaints	64.83 ± 12.44	64.69 ± 9.05	57.50 ± 6.89	67.30 ± 12.25	64.70 ± 13.03	59.40 ± 7.43
YSR Withdrawn/Depressed	63.25 ± 13.42	62.67 ± 8.71	56.00 ± 6.61	68.85 ± 12.84	62.47 ± 10.17	63.60 ± 13.45
YSR Anxious/Depressed	67.25 ± 10.95	70.25 ± 12.35	60.33 ± 9.94	65.75 ± 11.22	63.36 ± 12.88	58.18 ± 9.91
MAST Attraction to Death	2.99 ± 1.67	2.37 ± 0.87	2.30 ± 0.82	2.44 ± 0.80	2.51 ± 0.79	2.29 ± 0.82
MAST Repulsion by Life	2.68 ± 0.53	3.31 ± 2.35	2.31 ± 0.69	3.01 ± 0.74	2.96 ± 0.70	2.45 ± 0.96
MAST Attraction to Life	3.54 ± 1.61	2.99 ± 1.02	3.63 ± 0.75	3.45 ± 0.58	3.24 ± 0.80	3.58 ± 0.79
MAST Repulsion by Death	2.43 ± 1.76	2.57 ± 1.28	2.14 ± 1.28	2.59 ± 1.46	2.29 ± 2.19	1.83 ± 1.01
BUT-A GSI	2.96 ± 1.05	3.19 ± 0.94	2.48 ± 0.80	3.00 ± 0.82	3.18 ± 0.82	2.78 ± 0.96
BDI	17.23 ± 11.99	19.25 ± 13.62	9.31 ± 7.03	17.70 ± 11.52	17.47 ± 10.46	11.33 ± 8.64
BAI	17.69 ± 10.44	20.75 ± 15.64	12.29 ± 9.11	18.47 ± 11.60	16.53 ± 12.57	10.47 ± 10.72

Between-group comparisons were not performed as they were considered irrelevant to the objectives of the study.

Table 6. Longitudinal trend of psychological measurements

	T0	T1	T2	Time Effect (F)
YSR Total Score	62.94 ± 10.07	71.41 ± 12.36[a]	65.29 ± 13.39[b]	**9.80, *P* < .001**
YSR Externalizing	55.75 ± 8.91	55.48 ± 11.62	51.50 ± 11.00[a]	**4.51, *P* = .015**
YSR Internalizing	67.33 ± 11.61	67.00 ± 10.23	59.03 ± 9.79[a,b]	**14.65, *P* < .001**
YSR Aggressive Behavior	57.75 ± 6.52	57.52 ± 6.61	55.26 ± 6.39	2.71, *P* = .077
YSR Rule-Breaking Behavior	55.84 ± 6.26	57.30 ± 8.01	54.44 ± 5.60	2.38, *P* = .104
YSR Attention Problems	62.44 ± 9.26	62.41 ± 11.59	58.88 ± 11.23	2.19, *P* = .123
YSR Thought Problems	61.28 ± 11.67	60.41 ± 10.31	54.67 ± 6.78[a,b]	**7.45, *P* = .002**
YSR Social Problems	62.59 ± 9.02	62.30 ± 10.48	56.65 ± 8.48[a,b]	**12.92, *P* < .001**
YSR Somatic Complaints	66.38 ± 12.18	64.70 ± 11.47	58.69 ± 7.06[a,b]	**9.44, *P* < .001**
YSR Withdrawn/Depressed	66.75 ± 13.13	62.56 ± 9.37[a]	60.22 ± 11.43[a]	**7.86, *P* = .001**
YSR Anxious/Depressed	66.31 ± 10.97	66.54 ± 12.87	59.07 ± 9.80[a,b]	**11.82, *P* < .001**
MAST Attraction to Death	2.67 ± 1.24	2.45 ± 0.81	2.30 ± 0.81	2.17, *P* = .124
MAST Repulsion by Life	2.88 ± 0.67	3.12 ± 1.62	2.39 ± 0.85[b]	**3.71, *P* = .031**
MAST Attraction to Life	3.49 ± 1.10	3.13 ± 0.90	3.60 ± 0.76	2.26, *P* = .115
MAST Repulsion by Death	2.52 ± 1.56	2.42 ± 1.82	1.96 ± 1.12	1.48, *P* = .238
BUT-A GSI	2.98 ± 0.90	3.18 ± 0.86	2.66 ± 0.89[b]	**5.06, *P* = .010**
BDI	17.52 ± 11.52	18.26 ± 11.76	10.48 ± 7.95[a,b]	**10.45, *P* < .001**
BAI	18.13 ± 10.93	18.41 ± 13.90	11.24 ± 9.96[a,b]	**5.27, *P* = .008**

F values for time effects are reported together with their respective *P* values. Statistically significant effects are reported in bold.
[a]Significantly different from T0.
[b]Significantly different from T1.

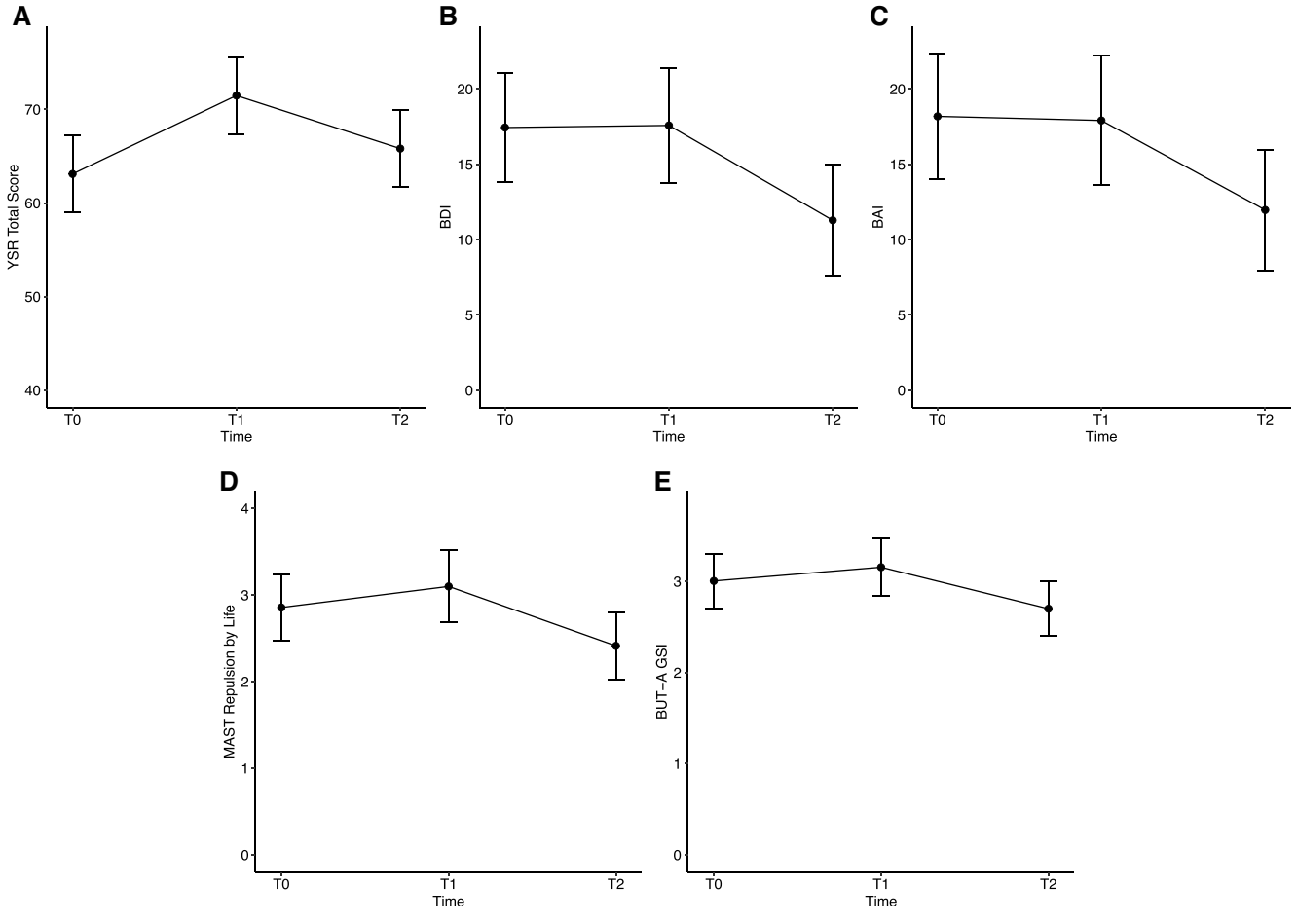

Figure 4. Longitudinal trends of YSR total score, BDI, BAI, MAST Repulsion by Life, and BUT-A GSI. Bars illustrate the range corresponding to 2 standard errors from predicted values.

growth percentile curves. A reduction in growth rate is a known effect of GnRHa treatment; however, this is expected to be temporary, considering the central role of sex hormones in the induction of the pubertal spurt, as demonstrated by recent studies both in AMAB and AFAB adolescents (20, 21). Significant weight and BMI increases were found in the AFAB group. Previous studies reported transient weight gain during GnRHa treatment (22, 51). There were no changes in blood tests in terms of HbA1c, transaminase, and lipid structure, except for a slight increase in HDL in AMAB subjects. Likewise, no significant changes in BP and waist and hip circumference were found. Other previous studies show similar data, except for HDL values which were found to be slightly reduced (22, 52).

Psychological Effects of GnRHa

Regarding psychological functioning, a reduction in both internalizing and externalizing problems was found upon GnRHa therapy, as shown by significant differences in psychological functioning (YSR) and depression (BDI) before and after the start of treatment. In particular, on average, internalizing YSR scored under the clinical cut off at T2. In the present study we also provide evidence for the first time that anxiety (BAI) and body image (BUT) significantly changed with GnRHa treatment. These findings are in disagreement with previous longitudinal studies (25, 26) in which anxiety and body image levels remained stable after 2 years of GnRHa use. Our results can be explained by the different aspects explored by the psychometric tools used. Indeed, the BAI (37) was used to assess State Anxiety, which refers to psychological and physiological transient reactions related to adverse triggering situations in a specific moment. In contrast, de Vries et al (25, 26) assessed a personality trait of anxiety (Trait Anxiety). We can speculate that State Anxiety could be more representative on how anxiety might work with TGDAs and, in particular, the decrease in anxiety could be explained with TGDAs being less worried about pubertal body changes while on GnRHa treatment. As far as body dissatisfaction is concerned, the unexpected changes observed after GnRHa treatment might be explained by the effect of treatment on body image concerns explored by the BUT. In fact, while satisfaction for individual body parts was not affected by GnRHa in previous studies using the Body Image Scale (25, 26), according to our results TGDAs were less worried about body changes once they started this medical treatment. It should also be considered that the BUT scale assesses the intimate relationship with one's own body than the distress caused by how one may appear to others (53, 54). These data stress the role of GnRHa treatment in reducing psychological distress and social difficulties when puberty moves in an unwanted direction (5, 12, 25, 55). Furthermore, the significant reduction in the "Repulsion to Life" MAST scale following the start of GnRHa treatment appears to be in line with previous literature, reporting an inversely proportional relationship between suicidal ideation and access to treatment

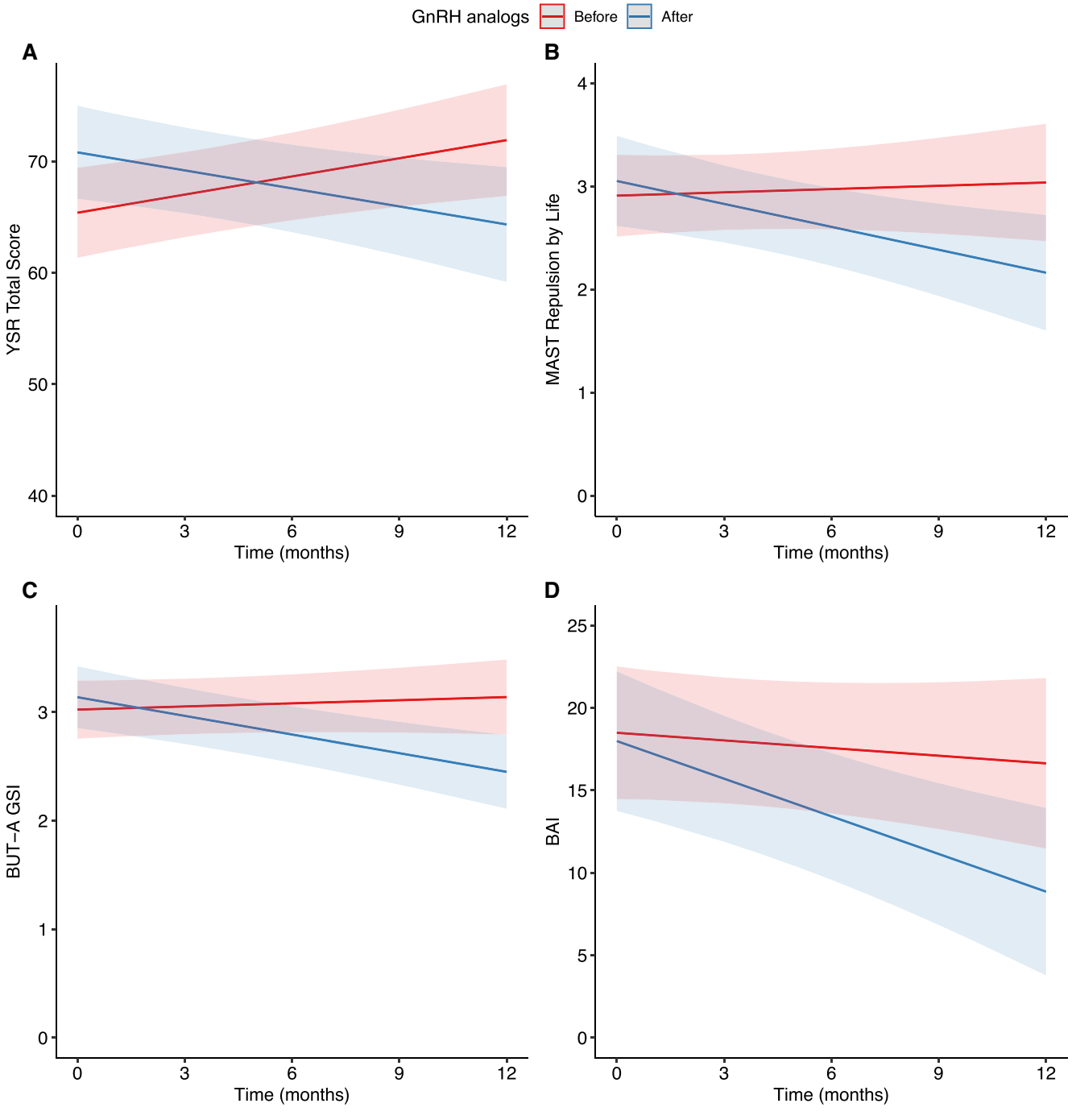

Figure 5. Longitudinal trends of psychopathological domains before and after GnRHa treatment. Ribbons illustrate the range corresponding to 2 standard errors from predicted values.

(56). Of particular interest is the initial statistically significant worsening in the total YSR score highlighted here. This seems to suggest an overall worsening of psychological functioning before the start of GnRHa treatment, then followed by a marked improvement after the start of therapy. The initial worsening could be explained as an exacerbation of GD in the peripubertal period, considering that in the absence of a GnRHa the bodily changes associated with puberty can gradually become more evident. We should also consider that adolescents present on average with an advanced Tanner stage and, therefore, with a strong desire to change some physical features. In line with this, psychological improvement—also of suicide risk (MAST), body uneasiness (BUT), and anxiety (BAI)—after the start of the GnRHa may be associated with the perception of having really started a medical gender-affirming path.

Correlation Between of Body Changes and Psychological Functioning

The longitudinal course of general psychological functioning, suicidal risk, and body uneasiness was positively associated with the physical effects and the hormone changes (height, BMI, hair growth, acne severity, reduction in plasma LH

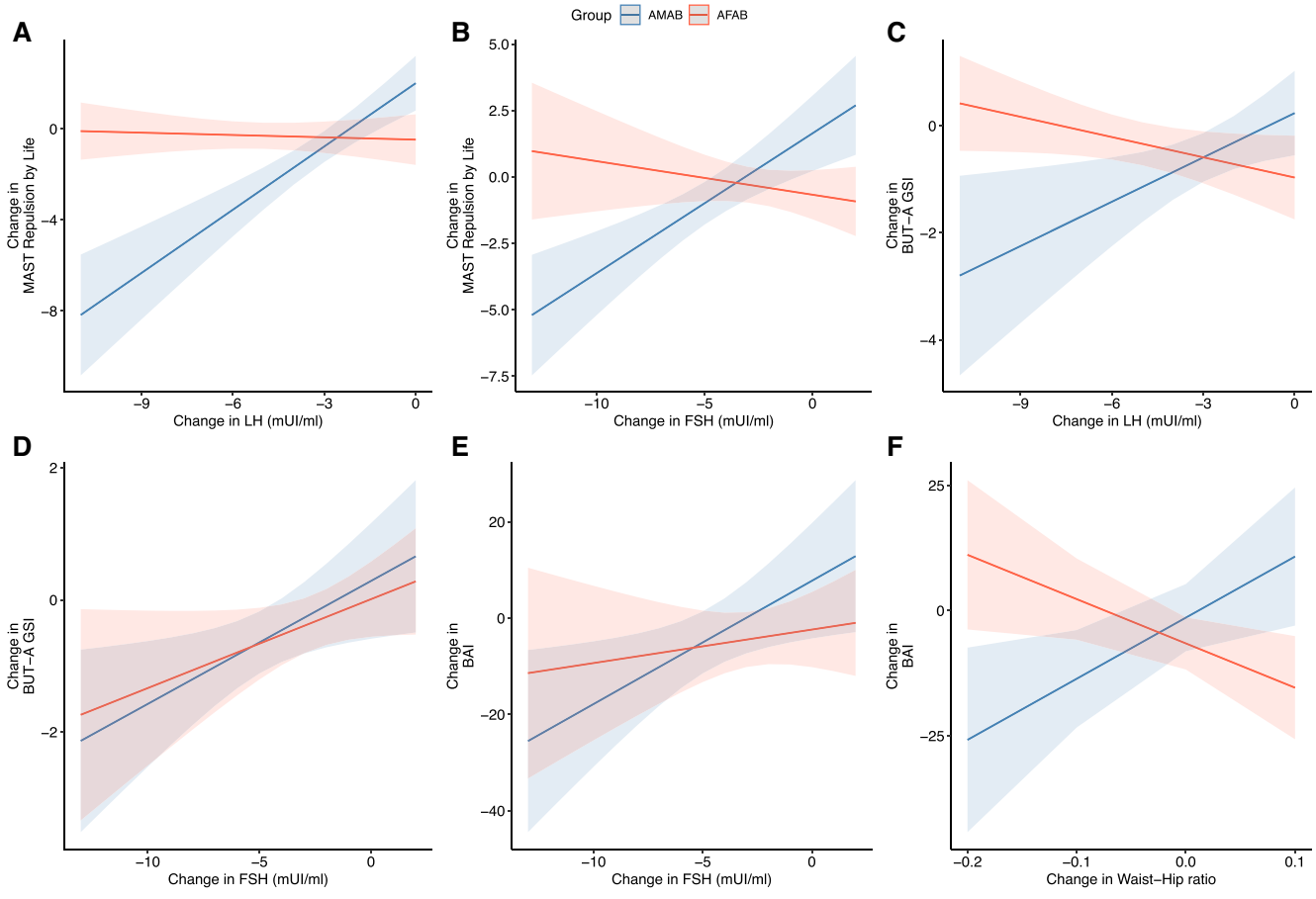

Figure 6. Correlations between endocrinological and psychometric modifications during GnRHa treatment. Ribbons illustrate the range corresponding to 2 standard errors from predicted values.

and FSH levels, waist circumference) of the GnRHa. These effects could be considered as being gender related, and the improvement in psychological functioning could be explained by those body changes being perceived as gender affirming, with the changes in gonadotropin levels being markers of an effectiveness in inducing such physical changes. In particular, reductions in both suicidal ideation and body uneasiness were more evident in the AMAB adolescent group. This could be explained as TGDA girls having more pressure to adhere to physical gender stereotypes or as a consequence of transphobic stigma that seems to affect TGDA girls more than TGDA boys. Previous studies had already documented the improvement in psychological functioning after body changes induced by gender-affirming hormonal treatment (57) and gender-affirming surgery (58, 59). This study underlines how this may also be happening regarding GnRHa treatment and may question the original rationale of this treatment that was originally developed as an extended evaluation phase. In particular, the use of a GnRHa was aimed at providing time for adolescents to think more calmly about their gender identity and about further gender-affirming steps (11, 12, 28). However, it has been recently reported that some TGDAs experience GnRHa treatment as the first formally necessary step of a seemingly clear trajectory towards further gender-affirming irreversible interventions (60). Also, the majority (93%) of TGDAs on a GnRHa requested to proceed with gender-affirming hormones later (61). In line with and considering that GnRHa treatment induces some body changes perceived as gender affirming, their use could represent the start of a medical gender-affirming path, especially in adolescents in the later stages of puberty.

Limits

The present study has several limitations. First of all, the small sample size (36 adolescents) could affect the statistical significance of the results, as multiple testing corrections were not considered feasible for this study. Furthermore, adolescents reported an advanced Tanner stage that could go beyond the rationale of the GnRHa as an extended evaluation phase. Indeed, GnRHa treatment was used in late puberty in order to stop menses in AFAB trans adolescents and to prevent further facial hair growth in trans AMAB adolescents, even though no regression of other physical sex characteristics was expected. On the other hand, one of the main findings of our study (even though it involved a very limited number of participants) is that some slight physical modifications induced by GnRHa treatment (ie, changes in waist–hip ratio) were associated with favorable outcomes in psychological functioning and body image in trans adolescents. However, most adolescents in late puberty would start hormonal treatment shortly after the start of GnRHa treatment, limiting concerns regarding a detrimental effect on bone health. Moreover, most AMAB adolescents were treated with a GnRHa as an antiandrogen therapy together with estradiol treatment in adulthood, in line with recent guidelines.

For late adolescents, there are no data to state whether and for what duration GnRHa therapy can be administered as a monotherapy without an impact on bone health (11, 62). Oral or injectable progestins (which are currently a second-line therapy, when GnRHas are not available or not indicated) might be a valid alternative to GnRHas in late puberty, especially in AFAB TGDAs. However, data about psycho-biological effects of progestins on TGDAs are still lacking. Moreover, depot medroxyprogesterone use in AFAB adolescents is associated with detrimental effects on healthy bone (63).

The assessment was based mainly on self-administered questionnaires that could affect the reliability of the answers: subjects may not have correctly understood the questions and, even if unintentionally, given the wrong answers. In interpreting the results of the YSR, MAST, and BUT-A measures in this population, it is important to note that there are no widely accepted guidelines or consensus to define what constitutes clinically meaningful changes for these psychometric outcomes. Thus, the significant changes observed in these measures should be assessed considering the study's specific context, population, and complementary findings rather than assuming a common point of clinical significance. Future research and expert consensus are needed to establish these benchmarks for clinical significance. The maximum follow-up duration was 12 months. Future studies with longer evaluations will be necessary to confirm these results and investigate the maintenance of the benefits obtained in the long term. Finally, for ethical reasons no comparison with a control group (TGDAs who are not given a GnRHa) was made, thus the study could not establish causality between the body changes provided by medical treatment and the psychological outcomes of the study participants. However, a randomized control study would raise ethical issues: transgender adolescent would have to face pubertal development regardless their psychological well-being, putting their psychological and physical health at risk.

Conclusions

This study shows the effectiveness of body changes induced by GnRHa treatment in alleviating psychological distress secondary to gender incongruence in a sample of Italian TGDAs. Interestingly, this study underlines how psychological functioning improves only following the first physical and hormone changes associated with the effects of GnRHa treatment. This seems to suggest that GnRHa treatment could be considered not only as an extended evaluation phase, but also as the start of a gender-affirming path (even if reversible).

Further studies on larger samples and with longer follow-ups are needed in order to evaluate the long-term effects of the use of a GnRHa. This study highlights once again the need for a multidisciplinary approach to the care of transgender health (11-13).

Author Contributions

A.D.F. and J.R. equally contributed to the manuscript. A.D.F. and J.R. contributed to the study conception and design. Material preparation, data collection and analysis were performed by A.R., E.C., F.M., C.C., M.P., M.M., V.R., M.M., L.V., G.C. The first draft of the manuscript was written by A.R., E.C., F.M., C.C. The manuscript was revised critically for important intellectual content by A.D.F., J.R., M.P., M.M., V.R., M.M., L.V., G.C. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A.D.F. and J.R. had directly accessed and verified the underlying data in the manuscript. S.D.A. reviewed the statistical analysis.

Disclosures

The authors declare that they have no conflict of interest.

Data Availability

Original data generated and analyzed during this study are included in this published article.

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Cureus

Open Access Review Article

DOI: 10.7759/cureus.36425

Suicide-Related Outcomes Following Gender-Affirming Treatment: A Review

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Review began 03/11/2023
Review ended 03/16/2023
Published 03/20/2023

Abstract

Gender-affirming treatment remains a topic of controversy; of particular concern is whether gender-affirming treatment reduces suicidality. A narrative review was undertaken evaluating suicide-related outcomes following gender-affirming surgery, hormones, and/or puberty blockers. Of the 23 studies that met the inclusion criteria, the majority indicated a reduction in suicidality following gender-affirming treatment; however, the literature to date suffers from a lack of methodological rigor that increases the risk of type I error. There is a need for continued research in suicidality outcomes following gender-affirming treatment that adequately controls for the presence of psychiatric comorbidity and treatment, substance use, and other suicide risk-enhancing and reducing factors. There is also a need for future systematic reviews given the inherent limitations of a narrative review. There may be implications on the informed consent process of gender-affirming treatment given the current lack of methodological robustness of the literature reviewed.

Categories: Psychiatry, Psychology, Epidemiology/Public Health
Keywords: suicide, transgender, suicide prevention, transgender youth, transgender health, transgender and gender-diverse, suicide risk

Introduction And Background

Gender-affirming treatment remains a topic of controversy, with many calling for greater access to gender-affirming treatments to foster psychological well-being for transgender, nonbinary, and intersex individuals [1-6]. There is accumulating literature that suggests transgender individuals suffer worse mental health outcomes than their cisgender peers; of particular concern is increased suicidality [4,7-13].

The literature to date reveals concerning trends regarding suicidality in transgender individuals. A high prevalence of suicide attempts and thoughts of suicide occur in transgender youth compared to their cisgender peers [11,12,14]. Transgender US military veterans have more than 20 times higher rates of suicide-related events than cisgender veterans [7]. The prevalence of suicidal ideation and attempts varies by sample [8], with the prevalence of suicidal ideation sometimes as high as 50-75% [4,10,15]. Rates of attempted suicide can reach peaks of 30% and above [4,14,15]. One longitudinal study of over 6,000 transgender individuals in the US indicates that the highest risk of suicide is among those under 18 years of age [9].

Transgender individuals are also at increased susceptibility for various suicide risk-enhancing factors, as a growing body of literature suggests that transgender individuals face a high burden of chronic health conditions [16,17], psychiatric illnesses and their comorbidities [18-20], substance use [21], trauma and victimization [20,22-24], and housing and employment discrimination [25].

In light of this high prevalence of suicidality and the proliferation of gender-affirming treatments, a common argument by advocates of gender-affirming treatments is that such treatments are needed to reduce suicidality [26-29]. This review is the first of its kind to evaluate mental health outcomes from gender-affirming treatments solely from the standpoint of suicidality, with the recognition that this evaluation of suicide-related outcomes pertains to transgender individuals as a single group; however, transgender and gender-diverse individuals comprise a heterogeneous population that may experience varying degrees of health outcomes and biopsychosocial stressors [20].

Review

Methods

On October 21, 2022, the following search strategy was used in PubMed: ("Suicide"[Mesh] OR suicid*[tiab]) AND ("Sex Reassignment Procedures"[Mesh] OR "sex change*"[tiab] OR "gender change"[tiab] OR "sex reassignment*"[tiab] OR gender reassignment*[tiab] OR "sex confirmation*"[tiab] OR "gender confirmation*"[tiab] OR "gender affirm*"[tiab] OR transitional surgery[tiab] OR "Gonadal Steroid Hormones"[Mesh] OR"Gonadotropin-Releasing Hormone"[Mesh] OR Hormon*[tiab]) AND ("Transgender Persons"[Majr] OR "Gender Dysphoria"[Majr] OR "Gender Identity"[Majr] OR transgender[tiab] OR "gender dysphoria"[tiab]

OR "gender identity"[tiab]) AND (following[tiab] OR after[tiab] OR outcome[tiab]).

The search terms resulted in 49 articles, of which the title and abstract were screened for inclusion. Included studies were required to be quantitative, peer-reviewed, published in English, and had an outcome measure of suicidal ideation and/or attempt after gender-affirming surgical procedures (hysterectomy, oophorectomy, mastectomy, phalloplasty, scrotoplasty, and breast, penile, or scrotal prosthesis), hormone treatment (including puberty-blocking treatment), and any combination thereof.

Out of screening the titles and abstracts of these 49 results for relevance, 19 were evaluated via full-text review for inclusion, of which 15 met the inclusion criteria. Based on references contained in the papers initially reviewed, the full text of an additional 11 papers was screened, with eight meeting the inclusion criteria (Figure *1*). The papers that met the inclusion criteria are grouped according to the type of gender-affirming treatment. Most studies that include surgery had patients on cross-sex hormones, but they used surgery as the designation of categorizing outcomes before and after an intervention (Table *1*).

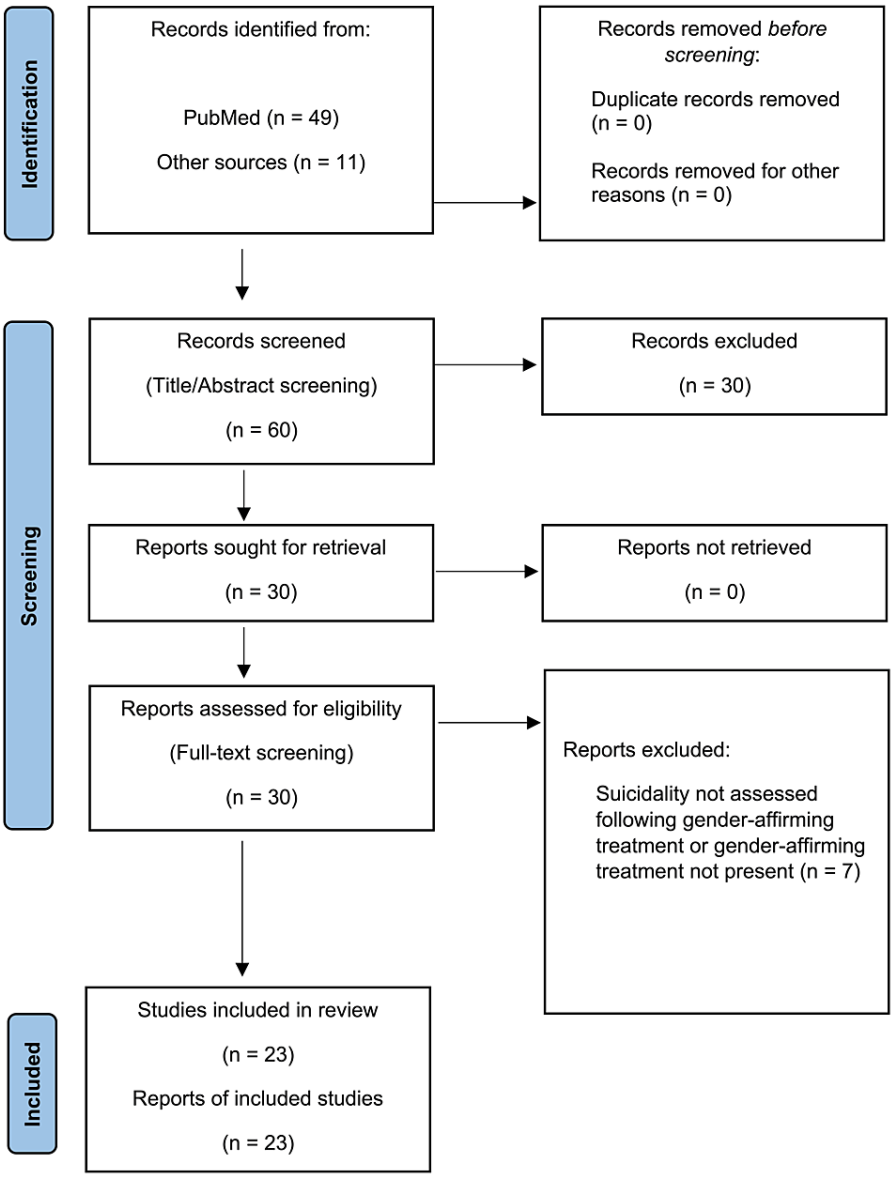

FIGURE 1: PRISMA flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

From: Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 372:n71. doi: 10.1136/bmj.n71 [30].

	Study type	Treatment type	Gender	Control for time elapsed since treatment	Before and after comparison	Within-groups or between-groups	Measure of statistical significance	Measure of effect size	Correction for multiple testing	Control for psychiatric diagnoses (axis I and II) or the presence of mood disturbance	Control for psychiatric treatment before or after gender-affirming treatment	Control for substance use or abuse	Control for other suicide risk-enhancing or risk-reducing factors	Accounts for death by suicide
Almazan and Keuroghlian (2021) [31]	Cross-sectional survey	Surgery	MtF, FtM, and nonbinary	No	No	Between-groups	Yes	Yes	Yes	Yes	No	No	Age, sex, gender identity, race/ethnicity, employment status, education, sexual orientation, family rejection, income, and health insurance status	No
Bränström and Pachankis (2020) [32]	Total population prospective	Combination or not specified	MtF and FtM	Yes	No	Within-groups	Yes	Yes	No	No	No	No	Legal gender, age, country of birth, education, urbanicity, and household income	No
Chaovanalikit et al. (2022) [33]	Prospective cohort	Surgery	MtF	Yes	Yes	Within-groups	Yes	No	No	No	No	No	No	No
De Cuypere et al. (2006) [34]	Retrospective cohort	Surgery	MtF and FtM	No	Yes	Within-groups	Yes	No	No	No	No	No	No	No
Dhejne et al. (2011) [35]	Population-based matched cohort	Surgery	MtF and FtM	No	No	Between-groups	Yes	Yes	No	No	Yes	Yes	Sex, age, immigration status, and inpatient psychiatric treatment	Yes
Glynn et al. (2016) [36]	Cross-sectional survey	Combination or not specified	MtF	No	No	Both	Yes	Yes	No	No	No	No	Age, ethnicity, and HIV status	No
Heylens et al. (2014) [37]	Prospective cohort	Combination or not specified	MtF and FtM	Yes	Yes	Within-groups	Yes	No	No	No	No	No	No	Yes
Hisle-Gorman et al. (2021) [38]	Retrospective cohort	Hormones (including puberty blockers)	Transgender and gender-diverse	Yes	Yes	Both	Yes	Yes	No	No	Total healthcare contacts per year	No	Sex, total healthcare contacts per year, age at gender-affirming treatment initiation, use of puberty blockers vs. gender-affirming hormones, and parental rank	No
Hughto et al. (2020) [39]	Cross-sectional survey	Combination or not specified	MtF and FtM	No	Yes	Within-groups	Yes	Yes	No	No	No	No	Age, education, and gender-related	No

													discrimination	
Hunt and Hampson (1980) [40]	Cross-sectional survey	Surgery	MtF	No	No	Within-groups	No	No	No	No	No	No	No	No
McNichols et al. (2020) [41]	Cross-sectional survey	Surgery	FtM	No	Yes	Within-groups	Yes	No	No	No	No	No	No	No
Park et al. (2022) [42]	Cross-sectional survey	Surgery	MtF and FtM	No	Yes	Within-groups	No	No	No	No	No	No	No	No
Rehman et al. (1999) [43]	Cross-sectional survey	Surgery	MtF	No	Yes	Within-groups	No	No	No	No	No	No	No	No
Rood et al. (2015) [44]	Cross-sectional survey	Combination or not specified	MtF and FtM	No	No	Between-groups	Yes	Yes	No	No	No	No	Age, race, ethnicity, education, and gender identity	No
Simonsen, Giraldi, et al. (2016) [45]	Retrospective cohort	Surgery	MtF and FtM	No	Yes	Both	Yes	Yes	No	No	No	No	No	Yes
Simonsen, Hald, et al. (2016) [46]	Retrospective cohort	Surgery	MtF and FtM	No	Yes	Both	Yes	Yes	No	No	No	No	No	Yes
Tordoff et al. (2022) [5]	Prospective cohort	Hormones (including puberty blockers)	MtF, FtM, and nonbinary	Yes	No	Between-groups	Yes	Yes	No	Yes	Yes	Yes	Self-reported gender, race, and ethnicity, self-report of conflict with parents due to gender identity or expression, and resilience	No
Tucker et al. (2018) [47]	Cross-sectional survey	Combination or not specified	MtF and FtM	No	No	Between-groups	Yes	Yes	No	Yes	No	No	Age, gender, race, and income	No
Turban et al. (2020) [48]	Cross-sectional survey	Hormones (including puberty blockers)	MtF and FtM	No	No	Between-groups	Yes	Yes	No	No	No	No	Age, gender identity, relationship status, family support, income, sexual orientation, education, and employment	No
Turban et al. (2022) [49]	Cross-sectional survey	Hormones (including puberty blockers)	MtF and FtM	No	Yes	Between-groups	Yes	Yes	Yes	No	No	No	Age, gender, sex, level of family support, sexual orientation, race/ethnicity, income, relationship status, education, employment, and harassment	
van der Miesen et al.	Cross-sectional	Hormones (including	MtF and FtM	No	No	Between-	Yes	Yes	Yes	No	No	No	Age, ethnicity, education, and	No

(2020) [50]	survey	puberty blockers)				groups						parent's marital status		
Wilson et al. (2015) [51]	Cross-sectional survey	Combination or not specified	MtF	No	No	Between-groups	Yes	Yes	No	No	No	No	Age and race/ethnicity	No
Zaliznyak et al. (2021) [6]	Cross-sectional survey	Hormones (including puberty blockers)	MtF and FtM	No	Yes	Within-groups	No	No	No	No	No	No	No	Yes

TABLE 1: Results

MtF: male-to-female; FtM: female-to-male.

Results

Combination or Not Specified

Hughto et al. (2020) utilized a cross-sectional, online survey of 288 US-based transgender adults via the Transgender Stress and Health Study. Bivariate and multivariable mixed-effect logistic regression analyses were used.

Participants were asked if they ever had a history of suicide attempt(s) or thoughts of suicide as a dichotomous variable before gender-affirming treatment. Prior to initiating unspecified gender-affirming treatment(s), 73.3% of the sample reported a history of suicidal ideation; this percentage dropped to 43.4% following the initiation of gender-affirming treatment. Prior to treatment initiation, 35.8% of the sample reported a history of suicide attempt(s), and 9.4% reported a history of suicide attempt(s) after initiation of gender-affirming treatment [39].

Adjusted multivariate analyses revealed greater odds of suicidal ideation (adjusted odds ratio (aOR), 3.86; 95% CI, 2.67-5.57; $p < 0.001$) and suicide attempt(s) (aOR, 5.52; 95% CI, 3.45-8.84; $p < 0.001$) before gender-affirming treatment compared to after [39]. Odds were adjusted for age, education, and gender-related discrimination. Potential interactions of psychiatric diagnostic history, psychiatric treatment after gender-affirming treatment, substance use, or time elapsed since gender-affirming treatment initiation were not evaluated.

Bränström and Pachankis (2020) conducted a total population study using the Swedish Total Population Register to evaluate the likelihood of mental health treatment following the initiation of hormone treatment or since the last surgical treatment. Hospitalization after a suicide attempt was the measure of suicidality implemented via the International Classification of Diseases, Tenth Revision (ICD-10) codes for intentional self-harm as a primary or secondary diagnosis. The population data from 2015 were utilized to avoid confounding by societal trends over time. As the primary outcome was the likelihood of mental health treatment as a function of time since the initiation of hormone treatment or since the last surgical treatment, the likelihood of mental health treatment that compared before and after gender-affirming treatment was not assessed.

Compared to the general population, transgender individuals had an increased odds of being hospitalized after a suicide attempt (aOR, 6.79; 95% CI, 4.45-10.35); however, a statistically significant relationship was not found for the odds of hospitalization after a suicide attempt after adjusting for the amount of time following the initiation of hormone treatment (aOR, 1.12; 95% CI, 0.97-1.30) or since the last surgical treatment (aOR, 0.87; 95% CI, 0.61-1.24) [32]. The odds ratios were adjusted for legal gender, age, country of birth, education, urbanicity, and household income. The odds ratios were not adjusted for any potential confounding by psychiatric diagnosis, psychiatric treatment besides inpatient hospitalization for a suicide attempt, or substance abuse.

In a subsequently published erratum, the authors noted no statistically significant difference in odds of hospitalization following a suicide attempt between transgender individuals matched by age, legal gender, education, and country of birth who had and who had not received any gender-affirming hormone or surgical treatment. The authors also reported that there was an absence of information that could be gathered on transgender individuals who died by suicide before 2015 [52].

Heylens et al. (2014) compared data from 57 Belgian transgender individuals before and after gender-affirming hormone treatment and surgery. Follow-up data were collected three to six months following the initiation of gender-affirming hormones and one to 12 months following gender-affirming surgery. Data on

the history of suicide attempt(s) and thoughts of suicide via a biographic questionnaire were collected for 54 patients before treatment and 42 patients provided data after treatment. The presence of a history of suicide attempt(s) did not reach statistical significance between data collection periods (p-values not provided). One patient died by suicide [37]. There was no accounting for any potential effect of psychiatric diagnostic differences, concurrent psychiatric treatment, substance use, or other suicide risk-reducing or enhancing factors.

Glynn et al. (2016) conducted a secondary analysis of data gathered from a sample of transgender women who engaged in sex work in California. A structured questionnaire was completed by 573 transgender women. Suicidality was measured by "a single dichotomous (yes/no) item ('Have you ever thought about committing suicide?')." Over half of the participants (56%) reported a history of ever experiencing suicidal ideation. Bivariate analyses revealed "no significant group differences among… surgery status or hormone use regarding endorsing suicidal ideation or not" [36].

A history of ever experiencing suicidal ideation was associated with "significantly lower levels of psychological and familial social affirmation than those who did not report lifetime suicidal ideation" via independent sample t-tests. Despite the statistically significant results, no correction for multiple testing was done for suicide-related outcomes following gender-affirming treatment (Tukey's tests were done for pairwise comparisons between racial groups), and effect sizes were not provided; however, they are likely small: receiving "psychological affirmation gender comfort" was associated with 0.5% fewer respondents experiencing suicidal ideation. Receiving "familial social affirmation satisfaction with family support" was associated with 0.11% fewer respondents experiencing suicidal ideation. Of the respondents, 2.89% were more likely to have a history of ever having suicidal ideation if they were of older age. Chi-square analysis demonstrated that white transgender women were more likely to have ever experienced suicidal ideation than other racial/ethnic groups.

Multivariate analyses demonstrated no statistically significant relationship between gender-affirmation treatments and a lifetime history of ever having suicidal ideation. Adjusted odds ratios showed a weak effect size with older age increasing the odds of ever having suicidal ideation. Adjusted odds ratios showed lower odds of ever having suicidal ideation among Latinas and Asian/Pacific Islanders, with Asian/Pacific Islanders having a larger effect size. There was no accounting of any potential confounding relationship of the results with psychiatric diagnostic history, concurrent treatment, substance use, or other suicide risk-reducing or enhancing factors besides age, ethnicity, or HIV status. The reporting of ever experiencing suicidal ideation as a dichotomous variable precluded any analysis of any relationship between the number of suicide attempts or frequency of suicidal ideation before and after any gender-affirming treatment.

Rood et al. (2015) utilized questionnaires from 350 transgender individuals in Virginia to evaluate the potential relationships between discrimination and transition status on suicide risk. Transition status according to the type and extent of treatment was not specified. Suicidality was measured by the question, ''Have you ever thought about killing yourself?'' as a dichotomous item. Regression analyses were adjusted for demographic variables; psychiatric diagnostic history was not ascertained by the questionnaire and thus was not controlled for [44].

Out of 350 individuals, 64.9% reported a history of ever experiencing suicidal ideation. Adjusted odds ratios revealed higher odds of a history of ever experiencing suicidal ideation in those who planned to pursue transition compared to those with no plan to receive treatment for transitioning (aOR, 2.85; $p < 0.01$). Those who lived full-time in their gender/had a full social transition had greater odds of ever experiencing thoughts of suicide compared to those with no plan to receive treatment for transitioning (aOR, 2.68; $p < 0.01$). Individuals who identified as female-to-male (FTM) had greater odds of ever experiencing thoughts of suicide compared to those who identified as male-to-female (MTF) (aOR, 2.48; $p < 0.01$). Compared to those who never experienced gender-related discrimination and had no plan to receive treatment for transitioning, those who experienced gender-related discrimination and either planned to receive gender-affirming treatment or were already living full-time as their identified gender had an increased odds of ever experiencing thoughts of suicide (aOR, 1.17; $p < 0.05$).

The authors interpreted these results by heavily relying on Meyer's minority stress model [53]. When discussing the limitations of the study, there was no mention of a lack of controlling for potential confounding variables of psychiatric diagnostic history, concurrent psychiatric treatment, substance use, or time elapsed since gender-affirming treatment. Furthermore, there was no discussion of the potential limitations on the validity and generalizability of the findings based on the statistical considerations: the adjusted odds ratio for the interaction of discrimination on suicide is of low magnitude (1.17) and vulnerable to the risk of type I error given the lack of controlling for confounding variables. Likewise, the adjusted odds ratios of increased risk of thoughts of suicide for those who lived full-time in their gender (2.68) and those who planned to pursue gender-affirming treatment (2.85) compared to those with no plan to pursue gender-affirming treatment, while of a moderate magnitude, are vulnerable to either type I error or a decreased magnitude given the lack of adequate controlling for confounding variables.

Wilson et al. (2015) conducted a secondary analysis on 314 surveyed transwomen in San Francisco to

compare the odds of various health outcomes according to the type of gender-affirming treatment. All but 22 of these individuals had gender-affirming treatment consisting of hormones, genital surgery, breast augmentation, or any combination thereof. Suicidality was measured as a dichotomous variable by asking the respondents if they had ever experienced thoughts of suicide [51].

Compared to those in the sample with no history of gender-affirming treatment, receiving treatment with hormones (OR = 0.2, 95% CI (0.1, 0.5)) or breast augmentation surgery (OR = 0.3, 95% CI (0.1, 0.6)) were associated with lower odds of ever having thoughts of suicide or attempting suicide. Individuals who received genital surgery did not have a statistically significant difference from those who did not receive gender-affirming treatment. The results were adjusted for age and race/ethnicity. There was no correction for any potential relationship with psychiatric diagnostic history, psychiatric treatment, substance use, or time elapsed since gender-affirming treatment, increasing the likelihood that the statistically significant results were vulnerable to a high risk of type I error.

Tucker et al. (2018) conducted a cross-sectional survey of 206 transgender veterans to compare outcomes among those who received a combination of gender-affirming hormones and surgery on both chest and genitals, hormone treatment only, hormone treatment and surgery on either chest or genitals but not both, and those with a history of no gender-affirming treatment. Participants were asked to rate the frequency of suicidal ideation from one (never) to five (very often or five or more times) within the past year. Respondents were also given question nine of the Patient Health Questionnaire-9 (PHQ-9) to assess suicidal thoughts over the previous two weeks at the time of the survey [47].

Mean scores were adjusted for age, gender, race, ethnicity, and annual household income. Analysis of covariance revealed statistically significant results with large effect sizes in lower past-year suicidal ideation for those receiving both genital and chest surgeries vs. those either receiving one surgery type only or gender-affirming hormones only ($\eta 2 = 0.051$). This pattern of results continued when analyzing suicidal ideation within the past two weeks, with the addition of there being lower scores of suicidal ideation that were statistically significant and with large effect size ($\eta 2 = 0.052$) for those with both genital and chest surgeries vs. no history of gender-affirming treatment.

An indirect-effects analysis was done to determine if the percentage of variance in suicidal ideation over the past two weeks between groups was due to the amount of depression over the past two weeks while controlling for covariates. An indirect effect was found for those receiving both chest and genitalia gender-affirming surgery vs. those who received no gender-affirming treatment; depression scores predicted 52.3% of the variance in suicidal ideation over the past two weeks. Similar indirect effects were found when comparing receiving surgery in one area alone or receiving gender-affirming hormones alone vs. receiving both chest and genitalia gender-affirming surgery. Psychiatric treatment, substance use, or other risk-reducing or enhancing factors for suicide besides age, gender, race, and income were not considered potential confounders.

Surgery

Chaovanalikit et al. (2022) conducted a prospective cohort study in which 37 transgender women in Thailand were assessed for quality of life and mental health outcomes before and after gender-affirming surgery. Suicidality was measured utilizing the Hamilton Depression Rating Scale (HAM-D). There were statistically significant improvements in quality of life, depression, and self-esteem. There was no correction for multiple testing, measures of effect size, or control for potential confounders such as psychiatric diagnosis, history of psychiatric treatment, substance use, or demographic variables. None of these patients reported suicidal ideation or attempts after treatment [33].

McNichols et al. (2020) conducted a survey of 246 transgender men who underwent any form of masculinizing/gender-affirming surgery at Johns Hopkins. Suicidality was assessed in the survey via the questions, “Do you have a history of any of the following? (check all that apply)” and “If you had any of the following prior to surgery, which of these have improved? (check all that apply)” with “Suicide Attempt” as an answer choice. A history of suicide attempt(s) was reported by 27% of respondents, and 14% of respondents reported an improvement, with $p < 0.003$. While the survey questions explicitly refer to “Suicide Attempt” as an indication of suicidality, the authors refer to improvements in “suicidal ideation” in the results section [41]. There was no indication of any measurement of the number of suicide attempts before and after masculinization procedures that were more specific than whether they “improved.” There was no accounting for diagnostic history that was clinically determined and verified beyond self-report, current or past psychiatric treatment, substance use, or any interaction of time elapsed since the masculinization procedure as potential confounders. There were no measures of effect size or correction of p-values for multiple testing.

Dhejne et al. (2011) conducted a population-based matched cohort study of 324 Swedish transgender individuals who underwent gender-affirming surgery with controls matched for age, biological sex, and who were residing in Sweden during the time the case person underwent treatment. Immigrant status and history of inpatient psychiatric treatment were more common among transgender individuals than controls, so

these were covariates in the calculation of hazard ratios. The two-sided significance value was set at 0.05, with no correction for multiple testing. The adjusted hazard ratio (aHR) of history of suicide attempt(s) among transgender individuals who underwent gender-affirming surgery was 4.9 (95% CI, 2.9-8.5) compared to matched controls across the entire time frame of the cohort (1973-2003). The odds of death by suicide were higher among transgender individuals who underwent gender-affirming surgery (aHR, 19.1; 95% CI, 5.8-62.9). The aHR was 7.9 (95% CI, 4.1-15.3) for the date range of 1973-1988. The aHR did not reach statistical significance for the period of 1989-2003 (aHR, 2.0; 95% CI, 0.7-5.3) [35].

Transgender women were more at risk of suicide attempt(s) than controls of either sex (aHR, 9.3; 95% CI, 4.4-19.9 for female and aHR, 10.4; 95% CI, 4.9-22.1 for male controls). Transgender men were more at risk for suicide attempt(s) compared to male controls (aHR, 6.8; 95% CI, 2.121.6), but the comparison to female controls did not reach statistical significance. The authors state, “[t]his suggests that male-to-females are at higher risk for suicide attempts after sex reassignment, whereas female-to-males maintain a female pattern of suicide attempts after sex reassignment.”

The authors did not correct for multiple testing. While psychiatric morbidity (including substance use) was controlled for in the form of a history of inpatient treatment, different psychiatric diagnostic categories were not taken into account as potential confounders. There was no consideration of any possible interaction of time elapsed since gender-affirming surgery. Most crucially, these findings refer to transgender individuals who received surgery compared to matched controls, not to these transgender individuals before their surgeries or to transgender individuals who have not undergone gender-affirming surgery.

Almazan and Keuroghlian (2021) conducted a secondary analysis of the 2015 US Transgender Survey (USTS). They evaluated 3,559 transgender individuals who underwent gender-affirming surgery of any kind, at least two years prior to responding to the survey. Suicidality was measured as dichotomous variables to whether a participant had thoughts of suicide or had a suicide attempt within the past year. Post-hoc analyses also evaluated the lifetime presence of suicidal ideation and suicide attempt(s). Undergoing gender-affirming surgery was associated with lower odds of suicidal ideation (aOR, 0.56; 95% CI, 0.50-0.64; $p < 0.001$) and lower odds of suicide attempt(s) (aOR, 0.65; 95% CI, 0.47-0.90; $p = 0.009$) within the past year compared to those who desired gender-affirming surgery but had not yet received it. The adjusted odds ratio for suicide attempt(s) did not reach statistical significance following the Bonferroni correction, which required a $p < 0.002$ [31].

Post-hoc analyses revealed that exposure to gender-affirming surgeries and lifetime measures of suicidal ideation or suicide attempt(s) did not reach statistical significance. Patients who received some of their desired gender-affirming surgeries had lower odds of suicidal ideation (aOR, 0.72; 95% CI, 0.63-0.81; $p < 0.001$) and suicide attempt(s) (aOR, 0.70; 95% CI, 0.53-0.93; $p = 0.01$) over the past year compared to those who desired gender-affirming surgery but had not received any, with past-year suicide attempts not reaching statistical significant following Bonferroni correction. Patients who received all of their desired surgeries had lower odds of suicidal ideation (aOR, 0.44; 95% CI, 0.38-0.51; $p < 0.001$) and suicide attempt(s) (aOR, 0.44; 95% CI, 0.28-0.70; $p < 0.001$) compared to those who desired gender-affirming surgery but had not received any. No interactions of history of mental health treatment besides gender-affirming counseling, substance use history, or time elapsed from surgery were utilized as potential confounders for initial and post-hoc analyses.

Park et al. (2022) conducted a postoperative survey of 15 patients who underwent gender-affirming surgeries from 1975 to 1989 at the University of Virginia. The postoperative data were compared to the preoperative data of 97 patients. Preoperative data revealed that 23.7% of the original sample had a history of suicidal ideation or suicide attempt(s). Of the 15 patients who responded to the postoperative survey, two reported a preoperative history of suicidal attempt(s); of those two, one reported a history of suicidal attempt(s) in the postoperative period. Eight of the 15 respondents reported a preoperative history of suicidal ideation; of these eight, one reported a history of suicidal ideation in the postoperative period [42].

There was no accounting for any possible interaction of psychiatric diagnostic history, psychiatric treatment, substance use, or other suicide risk-reducing or enhancing variables with suicidality. There was no significance testing or measure of effect size. A strength of the study was the gathering of long-term outcome data; however, contacting patients via phone to conduct the survey did not allow the authors to ascertain if any of the clinic’s patients died by suicide following the initial preoperative data collection.

De Cuypere et al. (2006) conducted a long-term follow-up study on 62 Belgians who had received gender-affirming surgery at the Gender Identity Clinic in Gent since 1986. A minimum of one year following surgery was an inclusion criterion for participation in the study. A semi-structured interview assessed suicidality via the rate of suicide attempts. Though not explicitly defined, the rate of suicide attempts was understood for the purposes of this review as the percentage of patients who had ever attempted suicide rather than the frequency of suicide attempts per person. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) axis I and II diagnoses were derived from the initial evaluation before surgery; it was unspecified if diagnostic revisions were made at long-term follow-up [34].

The suicide-attempt rate before gender-affirming surgery was 29.3%; following gender-affirming surgery, the suicide-attempt rate decreased to 5.1% (p = 0.004). The authors concluded that MTF patients attempted suicide as a means to cope with stress more frequently than FTM patients based on semi-structured interviews: “The postoperative male-to-females gave the following reasons for their suicide attempts: the end of a relationship (which they perceived as a challenge to their new gender), postoperative complications or an unease with their looks. They are more fragile when they are less credible in their new gender and when they have more pre-morbid psychiatric problems, especially personality disorders.”

Despite the claims made regarding the differences in the contributing factors for suicide attempts between MTF and FTM patients, there were no quantitative data used to support these findings. Despite the extensive gathering of various demographic and clinical data, even including data on social satisfaction before and after surgery and perceived credibility in one’s new gender, these data were not used to evaluate potential effects on differences in suicide outcomes. There was no controlling for any relationship between psychiatric diagnostic history, or the presence of psychiatric treatment on the rate of suicide before and after gender-affirming surgery was undertaken. There was no correction for multiple testing. A potential relationship of the amount of time elapsed since gender-affirming surgery on the rate of suicide was not assessed, though at least a minimum of one year had passed from surgery to the time of the survey.

Simonsen, Giraldi, et al. (2016) and Simonsen, Hald, et al. (2016) analyzed morbidity and mortality of Danish patients before and after gender-affirming surgery from 1978 to 2010. Both studies identified 104 individuals who had undergone gender-affirming surgery according to the Danish National Health Register. According to the Danish Register of Causes of Death, 10 of these 104 individuals had died following gender-affirming surgery from 1978 to 2014. Out of these 10 individuals, two had died by suicide at 19 and 26 years, respectively, following gender-affirming surgery. The studies discussed limitations from a small sample size, including insufficient statistical power [45,46]. Data concerning death by suicide or any other measure of suicidality before gender-affirming surgery were not compiled, preventing any before-and-after treatment comparison.

Rehman et al. (1999) conducted a follow-up study of 28 MTF individuals who had received gender-affirming surgery in New York from 1980 to 1997. Respondents had a minimum of three years post-surgery at the time of data collection. Suicidality was measured via a questionnaire by the item, “Did you have any suicidal thoughts or gestures before or after the surgery?” Two patients reported thoughts of suicide “shortly after surgery.” The authors noted a “marked decrease of suicide attempts” following surgery; however, their questionnaire did not ask about suicide attempts. It may have been that additional interviews were given [43]. Nonetheless, there was no indication that the data were collected through this method, and exact figures were not provided. One patient died by suicide in jail. A comparison via quantitative analysis of suicidality before and after gender-affirming surgery was not provided.

Hunt and Hampson (1980) conducted a follow-up study on 17 MTF individuals who underwent gender-affirming surgery. Two patients attempted suicide following surgery, within a year and six years after treatment, respectively. Both suicide attempts were in “response to the break-up of a relationship” [40]. No comparison of suicidality before and after surgery was undertaken, and the study would likely have been too underpowered to control for possible confounders of suicide risk-enhancing factors.

Hormones

Hisle-Gorman et al. (2021) conducted a retrospective cohort study of 3,754 transgender and gender-diverse (TGD) youth aged eight to 21 years of age in the US military healthcare system. Mental healthcare utilization of TGD individuals was compared before and after the initiation of gender-affirming hormones or puberty blockers. Mental healthcare utilization of TGD individuals was also compared to their cisgender siblings. Suicidality was measured by the presence of a diagnosis of suicidal ideation or self-harm (non-suicidal self-injury or self-harm with suicidal intent not specified). Odds ratios and incidence rate ratios were adjusted for sex, total healthcare contacts per year, age at gender-affirming treatment initiation, use of puberty blockers vs. gender-affirming hormones, and parental rank.

TGD youth had greater odds of receiving a diagnosis for suicidal ideation or self-harm than their siblings (aOR, 7.45; 95% CI, 6.11-9.08). About a quarter of the TGD cohort were on either puberty blockers or gender-affirming hormones. Data were analyzed to compare their mental healthcare utilization from roughly seven years prior to gender-affirming treatment with one-and-a-half years following treatment initiation. The adjusted incidence rate ratio of mental healthcare visits for suicidality was higher following the initiation of gender-affirming care (adjusted incidence rate ratio, 1.74; 95% CI, 1.18-2.56) [38].

The authors noted an increased use of neuroleptics by the transgender cohort, citing concern that the result meant that lack of gender-affirming care may lead to major depressive disorder with psychotic features. The question of whether off-label use of antipsychotics for what was actually comorbid personality pathology, particularly borderline personality disorder, was never addressed, despite that TGD youth had greater odds of a personality disorder diagnosis than their cisgender siblings (aOR, 2.54; 95% CI, 1.71-3.78) and the increasing recognition of personality disorders occurring in adolescence [54,55]. Had the presence of

personality disorders been controlled for, it is possible that the higher incidence rate ratio of mental healthcare visits for suicidality following initiation of gender-affirming treatment would not have reached statistical significance.

Tordoff et al. (2022) conducted a prospective, observational cohort study of 104 transgender and nonbinary persons aged 13-20 years at a Seattle gender clinic. Thoughts of self-harm or suicide were assessed via the PHQ-9 question nine; at baseline, 43.3% of patients reported thoughts of self-harm or suicide in the prior two weeks. Potential confounders included as covariates were temporal trends, self-reported gender, race, and ethnicity, ongoing psychiatric treatment, self-report of conflict with parents due to gender identity or expression, any substance use within the past year, and resilience.

Bivariate and multivariate analyses compared mental health outcomes from the 33.7% of participants who did not receive gender-affirming hormone treatment or puberty blockers and the 66.3% of participants who had by the end of 12-month follow-up. Bivariate analyses revealed an association of substance use with increased odds of thoughts of self-harm and suicide (aOR, 2.06; 95% CI, 1.08-3.93). The receipt of puberty blockers or gender-affirming hormones was associated with decreased odds of thoughts of suicide or self-harm (aOR, 0.47; 95% CI, 0.26-0.86). Temporal trends, self-reported gender, race, and ethnicity, ongoing psychiatric treatment, self-report of conflict with parents due to gender identity or expression, and resilience did not reach statistical significance.

Multivariate analysis demonstrated further reduced odds of thoughts of self-harm and suicide associated with the receipt of puberty blockers or gender-affirming hormones (aOR, 0.27; 95% CI, 0.11-0.65). There was an increased likelihood of thoughts of suicide or self-harm for those who did not receive puberty blockers or gender-affirming hormones at six months (aOR, 2.76; 95% CI, 1.22-6.26) but not at the other measured points in time.

This study provides fairly rigorous methods to control for confounding; in addition to the covariates accounted for in multivariate analyses, the authors employed E-value calculations to control for unmeasured confounding. In their supplementary attachment, they state that “the observed OR of 0.27 could be explained away by an unmeasured confounder that was associated with both the PB/GAH and the moderate to severe depression by a risk ratio of 3.25-fold each, above and beyond the measured confounders, but weaker confounding could not do so” [5]. The large effect size observed in this study warrants further investigation, particularly to determine how robust the effect would be after controlling for axis II diagnoses.

Zaliznyak et al. (2021) reviewed the age of first experiencing persistent gender dysphoria, age of social transition, and age of receiving gender-affirming hormone treatment in a sample of 155 transgender women and 55 transgender men in a Los Angeles clinic. All of these patients had socially transitioned and had received gender-affirming hormone treatment for at least a year. Their mental health histories were also taken. Out of the 55 transgender men, 21% had a history of at least one suicide attempt. The authors reported that out of those patients with a history of suicide attempt(s), 10% reported suicidal ideation after receiving gender-affirming hormone treatment or socially transitioning.

The authors appear to designate "Reported Current Feelings of Suicide Ideation" as whether suicidal ideation occurred after initiating gender-affirming hormone treatment or socially transitioning, thereby conflating the current reporting of suicidal ideation in a snapshot of time as the history of any suicidal ideation occurring after gender-affirming hormone treatment or socially transitioning. No patients reported suicide attempt(s) following gender-affirming hormone treatment or socially transitioning. There were no results given on the average amount of time following transitioning and suicide measures, nor were there tests of statistical significance.

The results for transgender women were reported similarly. Of 155 transgender women, 30% reported a history of suicide attempt(s); 27% of those who had a history of suicide attempt(s) reported current suicidal ideation (though later described as occurring after initiating gender-affirming hormone treatment or socially transitioning). No patients reported suicide attempt(s) following transitioning. There were no results given on the average amount of time following transitioning and suicide measures, nor were there tests of statistical significance.

The authors did not indicate whether they reviewed clinic records for any patients who died by suicide following gender-affirming hormone treatment or socially transitioning. There was no consideration of the effect of confounding diagnoses on the suicidality measures. Nevertheless, the authors conclude: “Given the high prevalence of suicidality, depression, and anxiety among transgender communities, it follows that proper measures should be taken to address the underlying condition – untreated GD [gender dysphoria]” [6].

Turban et al. (2022) examined data from over 21,000 transgender adults from the 2015 USTS. Suicidality was ascertained by inquiring whether there was any suicidal ideation with or without a plan, suicide attempt(s), or suicide attempt(s) requiring hospitalization over the year prior to the survey being taken. Individuals were

asked about various demographic and other confounding variables, but any current or prior mental health treatments besides hospitalization secondary to suicide attempt(s) were not gathered and controlled for.

Those who received gender-affirming treatment during adolescence and adulthood were compared to those who desired access to these treatments but never received them. Access to these treatments in early adolescence was associated with lower odds of suicidal ideation over the past year (aOR, 0.4; 95% CI, 0.2-0.6; $p < 0.001$) compared to those who desired but did not attain these treatments. For late adolescence (aOR, 0.5; 95% CI, 0.4-0.7; $p < 0.0001$) and for adulthood (aOR, 0.8; 95% CI, 0.7-0.8; $p < 0.0001$), there were also lower odds of suicidality over the year preceding the survey for those who had access to gender-affirming hormones during those periods of life [49].

Post-hoc analyses revealed that access to gender-affirming hormones during adolescence rather than adulthood was associated with lower odds of suicidality (aOR, 0.7; 95% CI; 0.6-0.9; $p = 0.0007$); there was no difference when comparing early vs. late adolescence. As mentioned, any current or prior mental health treatments besides hospitalization secondary to suicide attempt(s) were not gathered and controlled for. The authors tried to assess a potential confounding of mental-health differences within the sample by examining those who had a lifetime history of suicidal ideation but none over the past year. There were greater odds of a lifetime history of suicidal ideation (aOR, 1.4; 95% CI, 1.3-1.5; $p < 0.0001$) but none in the past year for those who accessed gender-affirming hormones in adulthood. Such a comparison in adolescence did not reach statistical significance.

The authors stated that a post-hoc analysis was done by examining those who had a lifetime history of suicidal attempt(s) but none over the past year; however, the results of such an analysis were not described. It is possible that assessing the confounding of mental-health differences by comparing suicidality over the past year to a lifetime history is insufficient. There will be a higher likelihood of the presence of lifetime suicidal ideation but none for the past year not just due to mental health differences but as a function of increased age, i.e., there is a possibility that those who received gender-affirming hormones 30 years ago have a higher chance of a lifetime history of suicidality compared to those who received such treatments five years ago. Additionally, older individuals may have the benefit of potentially having a longer period of time receiving mental health treatment, which may account for no suicidality over the past year. There was no information from those who died by suicide. Finally, there was no accounting for effects due to psychiatric diagnostic history.

Puberty Blockers

Turban et al. (2020) analyzed data from the 2015 USTS to include “3,494 individuals between the ages of 18 and 36 who ever wanted pubertal suppression as part of their gender-affirming medical care” as an adolescent. The results indicated that 89 (2.5%) of this sample received puberty blockers. Univariate analyses indicated lower odds of lifetime suicidal ideation as well as suicidal ideation within the past year for those who received puberty blockers. Multivariate analyses revealed that the receipt of puberty blockers “was associated with decreased odds of lifetime suicidal ideation” (aOR, 0.3; 95% CI, 0.2-0.6). Suicidal ideation within the past year did not reach statistical significance. Lifetime suicide attempts did not reach statistical significance depending on receipt of blockers in univariate analyses and thus were not assessed with multivariate analysis [48]. The presence of mental health treatment, substance use, or psychiatric diagnostic history was neither mentioned nor controlled for.

Van der Miesen et al. (2020) compared outcomes at a gender clinic in the Netherlands between a sample from the general population: 272 transgender adolescents at referral who had not begun puberty blockers, and 178 adolescents who were currently on puberty blockers. Suicidality was measured by items asking, “I deliberately try to hurt or kill myself” and “I think about killing myself” [50].

The control group and those who were currently on puberty blockers did not have any statistically significant difference in suicidality, whereas those who were referred to the clinic but had not begun puberty blockers scored higher in suicidality than the other groups, but Cohen’s *d* revealed small effect sizes. There was neither mention nor control for psychiatric diagnostic history, substance use, or current psychiatric treatment.

Discussion

The majority of the 23 studies reviewed claimed that various forms of gender-affirming treatment were associated with reductions in suicidality; however, the validity and robustness of their results suffered from either a lack of measures of statistical significance and effect size, correction for multiple testing, controlling for psychiatric diagnostic makeup or psychiatric treatment history, substance use, the interaction of time since receiving gender-affirming treatment, or any combination of these. The two studies that showed an increase in suicidality for those who received gender-affirming treatment suffered from many of the same problems in validity and robustness. Additionally, one of these studies did not compare suicidality outcomes before and after treatment but rather to the general population [35], and the other [38] yielded a small effect size that would likely constitute little clinical relevance; moreover, its results may not have

reached statistical significance if there was adequate controlling for confounders.

Controlling for a potential effect of psychiatric diagnoses or degree of mood disturbance was undertaken by three of the studies reviewed [5,31,47]. The need to control for comorbid psychiatric diagnoses or degree of mood disturbance is highlighted by the findings of Tucker et al. (2018). Through indirect analysis, they found that depression scores predicted over half of the variance in suicidality over the past two weeks before their sample responded to the survey. The lack of accounting for psychiatric comorbidity and other dynamic suicide risk-enhancing factors may be the greatest limitation in the body of literature to date regarding suicidality outcomes following gender-affirming treatment.

The presence, type, and timing of psychiatric treatment history represent a potential confounder that was not considered by the majority of studies. Three of the reviewed studies accounted for some form of psychiatric treatment [5,35,38]. Hisle-Gorman et al. (2021) controlled for the total healthcare contacts per year (inpatient and outpatient), Dhejne et al. (2011) controlled for inpatient psychiatric treatment, and Tordoff et al. (2022) controlled for "ongoing mental health therapy." There is accumulating evidence of the efficacy of psychiatric treatments that may lower the risk of suicide [56-58]. It would be beneficial for future studies to collect data for psychiatric treatment both before and after gender-affirming treatments.

Comorbid substance use has been well-documented as a concern for TGD individuals [19-21,59-61]. In addition to substance use being a dynamic risk factor for suicide [62,63], this relationship is borne out for TGD individuals as well [24]. Only two of the studies reviewed accounted for substance use [5,35], revealing a glaring risk of type I error in the literature, as access to gender-affirming treatment may or may not also serve as a proxy to access to other medical treatments, such as treatment for substance use.

Given that the 23 studies spanned a wide range of locations and dates conducted, it is not surprising that a uniform measure of suicidality was not employed across studies. An evaluation of the number of suicide attempts before and after gender-affirming treatment will likely be the most robust measure for suicidality rather than the presence and frequency of thoughts of suicide, particularly measures of suicidal ideation significantly limited in the expanse of time, such as the PHQ-9 question nine employed in Tordoff et al. (2022) and Tucker et al. (2018). A suicide attempt represents a more circumscribed occurrence, thus more easily and reliably quantifiable than thoughts of suicide; however, given that suicide attempts are a rarer phenomenon, the use of this outcome variable alone would yield less power and increase the risk of type II error. Nonetheless, the presence of thoughts of suicide at distinct points in time may be confounded by a diverse experience of such thoughts by individuals. For instance, individuals may be aware of a nearly ever-present sense of suicidal ideation, particularly in the presence of axis II pathology rather than a significant stressor or exacerbation of axis I pathology [64].

The potential confounding nature of utilizing the presence of suicidal ideation as the sole measure of suicidality may be reflected in the literature reviewed. For example, Almazan and Keuroghlian (2021) reported a lack of a statistically significant relationship between gender-affirming surgery and suicide attempts within the past year or the lifetime number of suicidal ideation. However, while there was not a statistically significant relationship with lifetime suicidal ideation, there was a statistically significant relationship with suicidal ideation within the past year. To have three measures of suicidality not reach statistical significance but suicidal ideation within the past year to reach statistical significance may represent multiple possibilities: suicidal ideation may be a more sensitive measure of suicidality as it is more prevalent and thus has more statistical power. Conversely, the presence of a high risk of type I error associated with recall bias and the potential inherent unreliability of suicidal ideation as a measurable construct may be detractors of its use. Finally, differing results according to suicidal ideation vs. attempts of suicide may represent the underpowered nature of the reporting of suicide attempts, which may represent the presence of a high risk of type II error.

The need for clear, objective reporting of suicide risk in transgender persons, including any change attributed to gender-affirming treatment, is highlighted further by the immense difficulty psychiatry as a field has in accurately predicting suicide risk. Even for at-risk populations, suicide attempts and parasuicidal behaviors are statistically rare enough to make it "impossible to predict on the basis of risk factors either alone or in combination" one's risk of suicide [65].

A dearth of high-quality studies that evaluate outcomes in suicide following gender-affirming treatment poses severe limitations on the extent of claims made during the informed consent process for gender-affirming treatment. An abundance of claims that are not backed by evidence does not represent quality empirical evidence but rather guidelines endorsed by various medical organizations. Just as in practice guidelines for the assessment and treatment of patients at risk for suicide, "practice guidelines do not represent the standard of care, much less for a fact-specific case in litigation" [66].

Clinical judgment, rather than an indiscriminatory tabulation of risk-enhancing factors for suicide, will ultimately be needed, as "no study has identified one specific risk factor or set of risk factors as specifically predictive of suicide or other suicidal behavior" [65]. Risk-enhancing factors for suicide may act in a synergistic manner, with mood disorders, substance use, physical and sexual abuse, minority sexual

orientation, disturbed family relationships, parental psychopathology, and various precipitating stress events [67] leading to near-infinite permutations of suicide risk that is ultimately expressed and unique on an individual level. This is especially the case for TGD individuals, for they constitute “heterogeneous groups of individuals with multiple intersecting identities” [20,59] that may contribute to different levels of risk for suicide.

Such permutations of suicide risk reinforce the need to control for various confounders, which is pervasively lacking in the literature to date. Most studies have ignored complex relationships among various risk factors for suicide, despite literature that suggests a nuanced intersection of these factors with suicide, such as victimization and substance use [24]. Given the heterogeneity of risk factors for this population [20,59], adequate control for confounding variables is needed to represent as accurately as possible the variance that can be attributed to gender-affirming treatment on suicide-related outcomes for transgender individuals as a whole and according to other defining characteristics.

In addition to trauma and abuse, other psychosocial stressors, “such as sudden unemployment, interpersonal loss, social isolation, and dysfunctional relationships, can increase the likelihood of suicide attempts as well as increase the risk of suicide” (“Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors,” 2006). It is notable that Tordoff et al. (2022) reported that conflict with caregivers over gender identity did not have a statistically significant relationship with thoughts of suicide, whereas Glynn et al. (2016) reported a statistically significant increase in suicidal ideation for those with less affirmation by one’s family. Additionally, Almazan and Keuroghlian (2021) reported lifetime suicide attempts and thoughts of suicide were not statistically significant with familial rejection as a covariate, potentially meaning that familial rejection accounted for some of the variances in suicide risk. The variety of findings regarding any potential effect of familial conflict on suicide may represent type I error, the unreliability of thoughts of suicide as a measure compared to suicide attempts, and/or the heterogeneous nature of the TGD population.

The collection of data that includes long-term follow-up is ideally suited to take into account the effects of a transgender individual’s time course, which may include a “honeymoon period” after receiving gender-affirming treatment [34]. Equally important is the controlling of time elapsed before and after gender-affirming treatment with regards to suicidality; otherwise, the number of suicide attempts or frequency of thoughts of suicide may be falsely lowered if the relative time after gender-affirming treatment is less than the pre-treatment period. However, the majority of studies did not control for the amount of time elapsed.

Limitations

The limitations inherent in a narrative review format are noted, particularly the absence of a second, independent reviewer for the inclusion and exclusion of studies as well as the lack of a systematized evaluation of publication bias and methodological rigor. Moreover, a single database was utilized, albeit with fairly extensive search criteria. Future systematic and/or scoping reviews are needed. Finally, this review may have limited generalizability. The studies included in this review span multiple countries, cultures, and decades; furthermore, TGD individuals comprise a heterogeneous group.

Conclusions

There is a need for continued research on suicidality outcomes following gender-affirming treatment. Future research that incorporates multiple measures of suicidality and adequately controls for the presence of psychiatric comorbidity, substance use, and other suicide risk-enhancing factors is needed to strengthen the validity and increase the robustness of the results. There may be implications for the informed consent process of gender-affirming treatment given the current lack of methodological robustness of the literature reviewed.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

I wish to thank Dr. Glatt and Dr. Slutzky for their suggestions and advice.

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Child and Adolescent Mental Health

Child and Adolescent Mental Health Volume **, No. *, 2020, pp. **–** doi:10.1111/camh.12437

Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature

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Background: Increasingly, early adolescents who are transgender or gender diverse (TGD) are seeking gender-affirming healthcare services. Pediatric healthcare providers supported by professional guidelines are treating many of these children with gonadotropin-releasing hormone agonists (GnRHa), which reversibly block pubertal development, giving the child and their family more time in which to explore the possibility of medical transition. **Methods:** We conducted a critical review of the literature to answer a series of questions about criteria for using puberty-blocking medications, the specific drugs used, the risks and adverse consequences and/or the positive outcomes associated with their use. We searched four databases: LGBT Life, PsycINFO, PubMed, and Web of Science. From an initial sample of 211 articles, we systematically reviewed 9 research studies that met inclusion/exclusion criteria. **Results:** Studies reviewed had samples ranging from 1 to 192 ($N = 543$). The majority (71%) of participants in these studies required a diagnosis of gender dysphoria to qualify for puberty suppression and were administered medication during Tanner stages 2 through 4. Positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage. One study met all quality criteria and was judged 'excellent', five studies met the majority of quality criteria resulting in 'good' ratings, whereas three studies were judged fair and had serious risks of bias. **Conclusion:** Given the potentially life-saving benefits of these medications for TGD youth, it is critical that rigorous longitudinal and mixed methods research be conducted that includes stakeholders and members of the gender diverse community with representative samples.

Key Practitioner Message

- Increasing numbers of early adolescents who are transgender or gender diverse (TGD) and seeking professional help.
- Pubertal development may lead to (a) greater anxiety about sexual identity and (b) suicidal thoughts among TGD.
- Professional organizations, such as the Endocrine Society and the World Professional Association for Transgender Health (WPATH), have recommended the use of puberty-blocking hormones to arrest pubertal development, thus allowing early adolescents and their families more time to consider the possible outcomes of gender reassignment.

What is new?

- This article is a report of a critical and systematic review of literature about the use of puberty-blocking hormones among TGD, the positive, and the negative outcomes associated with their use.
- The findings of this systematic review can guide healthcare professionals in their discussions with TGD youth and their families as they consider the risks and benefits of puberty suppression.

What is significant for clinical practice?

- A summary of current research on the use of puberty-blocking hormones suggests that clinicians follow the guidelines offered by the Endocrine Society and WPATH to enhance the positive outcomes associated with use of these medications.
- Clinicians and researchers should work together to conduct well-designed and rigorous longitudinal and mixed methods studies of TGD youth using GnRHa.

Keywords: Transgender; adolescent; puberty blockers; critical review

Published by John Wiley & Sons Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main St, Malden, MA 02148, USA

Introduction

Recently, there has been an increase in the number of parents seeking medical advice and care for their early adolescent children who are transgender or gender diverse [TGD] (Bonifacio & Rosenthal, 2015; Turban, 2017). A study of a representative sample of middle school youth in San Francisco using the Youth Risk Behavior Survey (YRBS) showed that 1.3% self-identified as transgender (Shields et al., 2013); in the 2017, YRBS data collected from a nationally representative sample of high school students ($N = 131{,}901$), 1.8% responded 'Yes, I am transgender', and another 1.6% responded, 'I am not sure if I am transgender' (Johns et al., 2019, p. 68). Compared to their cisgender peers, these gender diverse youth bear a disproportionate burden for mental health problems including substance use and suicide attempt (Lowry et al., 2018).

Hormonal treatment, including the use of puberty suppressing drugs, provides a potentially life-saving solution for these patients, yet for this specific population of patients, the long-term consequences of these drugs are relatively unknown (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2015). For children and adolescents who experience gender dysphoria (GD), the possibility of receiving this treatment provides hope; however, the lack of longitudinal evidence may lead to barriers in accessing and receiving treatment. Two groups, the World Professional Association for Transgender Health (WPATH, s2011) and the global Endocrine Society in the United States (Hembree et al., 2009, 2017), have provided consensus expert guidelines for the use of puberty-blocking agents in children and early adolescents with GD. The use of these medications, in many early pubertal children, is an important component of gender-affirming care (Edwards-Leeper, Leibowitz, & Sangganjanavanich, 2016). These consensus guidelines have been critical in supporting the work of medical professionals who are balancing clinical judgment and evidence-based research in the care of these patients.

In a descriptive study of the physiological and psychological characteristics of 101 transgender youth between the ages of 12 and 24 years, Olson, Schrager, Belzer, Simons, and Clark (2015) found that these youth were aware of their gender incongruence at a mean age of 8.3 ± 4.5 years, over one-third experienced symptoms of clinical depression, and over half reported having suicidal thoughts at least once and about one in three had made one or more suicide attempts. Liu and Mustanski (2012) followed a community sample of 246 LGBT youth between the ages of 16 and 20 years prospectively and found that previous victimization predicted both self-harm and suicidal ideation. Clearly, the risk of adverse mental and physical outcomes among this population of youth is high. Thus, the need to find a way to prevent such dire consequences is equally high.

Researchers in the Netherlands conducted a qualitative study of 13 early adolescents (five trans girls and eight trans boys) and explored the perceptions of these adolescents (average age of 16 years 11 months) and the professional teams working with them about the use of puberty suppression in the form of gonadotropin-releasing hormone agonists (GnRHa) (Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2016). Themes derived from interviews with these adolescents were that relative to using GnRHa for puberty suppression, (a) it is difficult to determine the appropriate age for starting the use of these hormones, (b) long-term effects of using suppression are unknown, and (c) both stereotypes and greater media attention create a social context that can be positive or negative. These themes were compared with data collected previously from professionals working with TGD youth and results in that study revealed that professionals worried more about long-term effects than did the youth, yet the youth worried more about the appropriate age for starting puberty suppression.

The advantages of using puberty suppression in children and adolescents with gender dysphoria have been identified as improving some psychological functioning such as decreased depression and improved global functioning. Identified disadvantages were unpleasant side effects such as hot flashes in AFAB youth treated later in puberty (e.g., Tanner stages 4–5), decreased growth velocity, and increased body mass index (Chew, Anderson, Williams, May, & Pang, 2018). In addition, bone turnover and bone mineral density have been shown to decrease with use of GnRHa, particularly in young transwomen (Vlot et al., 2017). A significant barrier to use of puberty suppressing medications is the high cost of the medications with insurance coverage for treatment of GD in children and early adolescents being highly variable and, in some cases, specific insurance plan exclusions (Stevens, Gomez-Lobo, & Pine-Twaddel, 2015).

The use of puberty suppressing drugs (e.g., gonadotropin-releasing hormone agonists or GnRHa) has long been viewed as the standard of care for children with central precocious puberty (Lee et al., 2014) and adverse physical and psychological effects have been rare (Krishna et al., 2019; Yu, Yang, & Hwang, 2019). GnRHa have also been used in adolescent females with endometriosis with mixed results (DiVasta & Laufer, 2013; Gallagher et al., 2018). Although these uses are beyond the scope of this review, it is important to acknowledge that risks and benefits among these disparate populations could differ.

Purpose

Despite the increase in demand for more healthcare services for TGD youth, research is still in its relative infancy. The purpose of this critical review is to present the current state of research on the use of puberty-blocking hormones in prepubescent TGD children/early adolescents.

Method

As authors of this review, we followed a seven-step method for critical reviews of the literature described by Cooper (2017). The seven steps are as follows: (a) formulate the problem; (b) search the literature; (c) gather information/data from the published studies; (d) evaluate the quality of the studies found; (e) analyze and integrate outcomes of the studies; (f) interpret the evidence found; and (g) present the results. Because there were no human subjects involved, we did not request institutional review board approval. We adhered to the Preferred Reporting

Items for Systematic Reviews and Meta-Analysis (PRISMA) as a guideline for reporting our process and displaying our decision points as shown in Figure 1 (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

Problem identification

The problem addressed in this review was identified in the introduction as a lack of knowledge about (a) the criteria for using puberty-blocking drugs; (b) the known risks associated with use of these drugs; and (c) the benefits of using such drugs with early adolescents. We specifically sought to answer the following questions relative to TGD early adolescents:

1 What prerequisite criteria (e.g., diagnosis of gender dysphoria; Tanner stage of sexual maturation) are being met before physicians administer gonadotropic-releasing hormone agonists (GnRHa)?

2 What specific drugs are used to suppress puberty in early adolescents?

3 What are the known risks and adverse outcomes of using GnRHa in early adolescents?

4 What have been the positive outcomes of using puberty suppression drugs in early adolescents?

Inclusion/exclusion criteria and literature search

Inclusion/Exclusion Criteria: Our inclusion criteria were that articles had to be either qualitative or quantitative research papers, written in English with a focus on the use of puberty-blocking drugs/hormones in early adolescents (e.g., ages 10–14) who self-identified as transgender or who had a medical diagnosis of gender dysphoria. The researchers had to identify risks and/or benefits associated with the use of these medications. Our exclusion criteria were editorials, letters to the editor, systematic reviews, and opinion pieces.

We consulted a health sciences librarian skilled in searching the literature on healthcare topics. She performed the search using four relevant and accessible databases: LGBT Life,

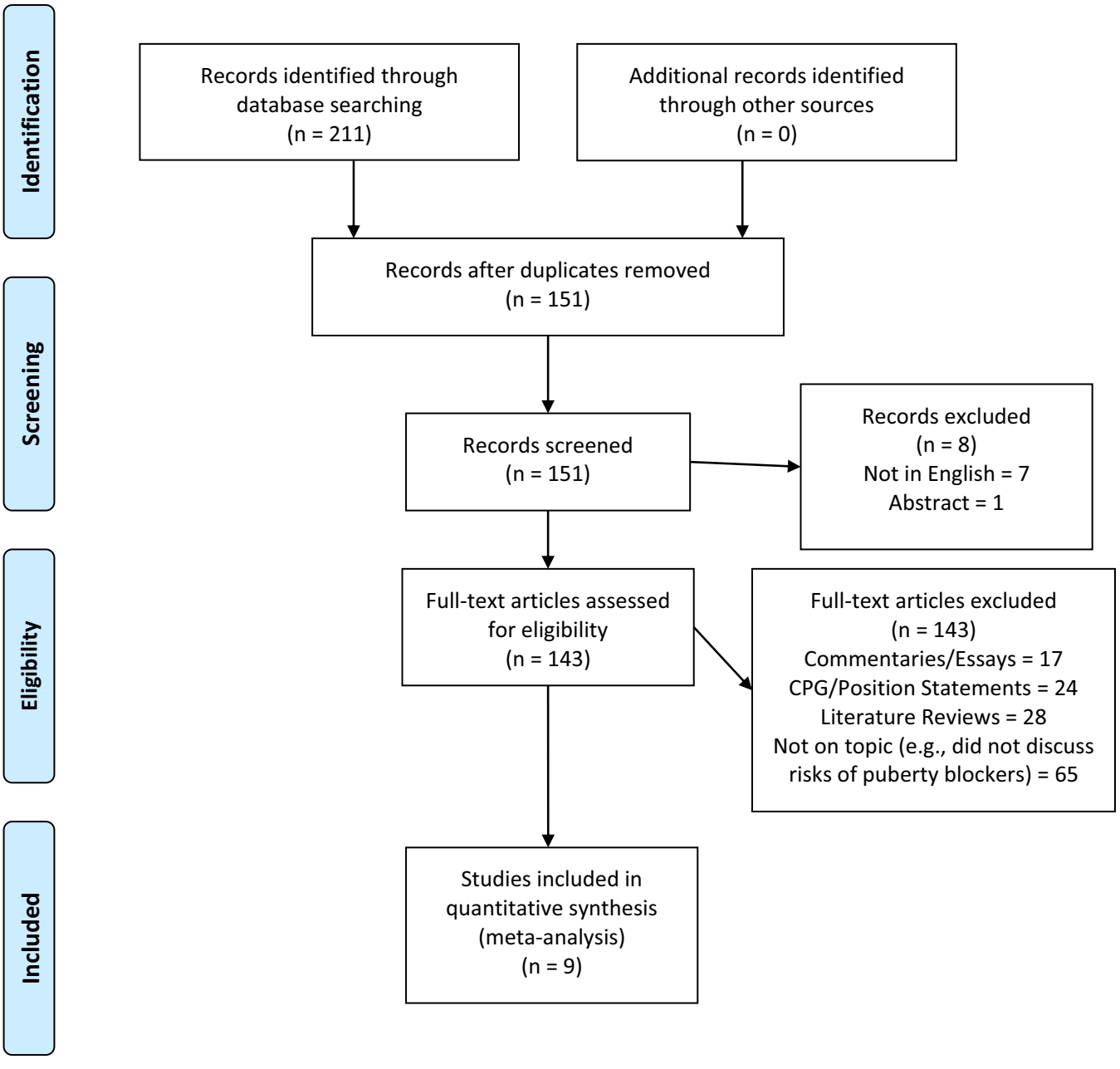

Figure 1. PRISMA flow diagram. CPG, Clinical Practice Guidelines

PsycINFO, PubMed, and Web of Science. Search strategies were composed for each database, using subject headings and keywords to recover articles on transgender persons and puberty blockers, puberty suppressors, or puberty inhibitors. Table 1 details the search terms for each database.

Our search resulted in a sample of $N = 211$ (Figure 1). We first removed duplicates, then divided the identified articles evenly among the first three authors. Using a screening checklist designed specifically for this review, we examined the abstract and the entire published paper to answer the following questions:

1 Was the paper written in English?
2 Was the focus of the paper on transgender youth/children or prepubescent children/early adolescents with gender dysphoria?
3 Did the article focus on the use of puberty-blocking drugs/hormones such as gonadotropin-releasing hormone analog (GnHRa)?
4 Did the authors identify risks and/or benefits associated with the use of these hormones?
5 Did the study use a qualitative or quantitative research design?
6 Was the paper a systematic or integrative literature review?

All papers for which the first five questions were answered affirmatively and the last question was not, were retained for full review.

Data extraction

After screening the articles, we developed a data extraction tool that included the name of the first author and date of the publication, the purpose of the study, a description of the sample (e.g., number and age of participants), prerequisites identified prior to use of puberty-blocking drugs, the names or types of drugs used, the youth's Tanner stage at the time the drugs were first administered, identified risks or adverse outcomes, positive outcomes, and our quality assessment value (see details below, in Step Four). We then extracted data from each article included to describe our sample and to address our research questions.

Evaluation of quality of studies

To determine the quality of each paper, two authors independently completed a checklist for each of the studies, compared their ratings and discussed differences until coming to consensus. We used one of three checklists, depending on the type of study design, to evaluate the quality of the information found in our literature sample and to report any type of bias found in the process. The three checklists were specific for evaluating the quality of retrospective chart reviews (Vassar & Holzmann, 2013), Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional and observational studies, and the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018). In assessing the quality of retrospective chart reviews, we created a checklist with the 10 questions specified by Vassar and Holzmann (2013) and arbitrarily created ratings of *poor* (1–3 yes answers), *fair* (4–6 yes answers), and *good* (7–10 yes answers). In using the JBI checklists, we computed a percentage of met criteria to determine quality and followed the same rating categories of *poor, fair,* and *good*. For all checklists used, if all criteria were met, the study was given a rating of *excellent*.

Analysis of outcomes and interpretation of evidence

Data analyzed for the nine articles included in this review were derived from retrospective chart reviews, case reports, a cross-sectional study, and prospective, observational studies. Thus, no statistical analysis nor meta-analysis could be done. Rather,

Table 1. Terms used to search four databases related to use of puberty blockers for early adolescents

Step	Term(s)
Database: LGBT Life	
1	puberty
2	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
3	1 AND 2
Database: PsycINFO	
1	transgender OR gender nonconforming OR nonbinary
2	puberty
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	1 AND 4
Database: PubMed	
1	('Transgender Persons'[Mesh] OR transgender [Title/Abstract] OR gender [2:17PMitle/Abstract][9:27 AMitle/Abstract] OR nonbinary[Title/Abstract]
2	puberty[Title/Abstract] OR prepuberty[Title/Abstract] OR prepubertal [Title/Abstract] OR prepubescent[Title/Abstract] OR prepubescence[Title/Abstract]
3	blocker[Title/Abstract] OR blockers[Title/Abstract] OR suppressor[Title/Abstract] OR suppressors[Title/Abstract] OR inhibitor [Title/Abstract] OR inhibitors[Title/Abstract] OR hormone suppressor[Title/Abstract]
4	bicalutamide[Title/Abstract] AND anastrozole [Title/Abstract]
5	3 OR 4
6	2 AND 5
7	'Gonadotropin-Releasing Hormone'[Mesh] OR gonadotropin- Releasing hormone[Title/Abstract] OR GnRH[Title/Abstract] OR histrelin[Title/Abstract] OR leuprorelin[Title/Abstract]
8	6 OR 7
9	1 AND 8
Database: Web of Science	
1	transgender OR gender nonconforming OR gender nonconforming OR nonbinary
2	puberty OR prepuberty OR prepuberty OR pubescent OR pubescence
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	gonadotropin-releasing hormone OR GnRH or histrelin OR leuprorelin
6	bicalutamide OR anastrozole
7	5 OR 6
8	4 OR 7
9	1 AND 8

data derived to answer our research questions are presented in the next step showing our results.

Results

Our searches yielded a total of 151 unique articles (after all duplicates were removed) related to the search terms. Details of the nine articles retained for review are in Table 2; all were published recently, between 2011 and 2020. Of these, four articles were retrospective chart reviews, two were case reports, one was cross-sectional, one was a prospective study to evaluate the efficacy and safety of using a GnRHa (triptorelin) drug over time in transgender adolescents (Schagen, Cohen-Kettenis, Delemarre-van de Waal, & Hannema, 2016). Sample sizes in these studies ranged from 1 to 192. The samples were 9–35 years of age and included a total of 296 transgender females, assigned male at birth (AMAB) and 404 transgender males, assigned female at birth (AFAB) and 2 who were undecided patients assigned male at birth ($N = 702$). Race/ethnicity was not reported in 6/9 (66.7%) of the studies reviewed. In the other three studies, the vast majority of the samples (96%, 83.5%, and 68.5% respectively) were Caucasian/White.

Prerequisite criteria

The prerequisite criteria that were met before physicians administered GnRHa drugs to early adolescents were not reported in four of the studies (Klaver et al., 2018; Nahata, Quinn, Caltabellotta, & Tishelman, 2017; Turban, King, Carswell, & Keuroghlian, 2020; de Vries, 2011). Other criteria mentioned were as follows: (a) being screened by a mental health professional who made a diagnosis of gender dysphoria (Khatchadourian, Amed, & Metzer, 2014; Vlot et al., 2017); and (b) diagnosis of gender identity disorder or lifelong extreme gender dysphoria and living in a supportive environment (Cohen-Kettenis, Schagen, Steensma, DeVries, & Delemarre-van de Waal, 2011; Schagen et al., 2016); and (c) gender dysphoria and gender incongruence (Schneider et al., 2017).

Table 2. Articles in a critical review of literature on use of puberty blockers in prepubescent child

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
Cohen-Kettenis et al. (2011)	Case report to describe a 22-year follow-up of FtM treated with GnRH analogs at age 13.	$N = 1$ AFAB; age 35 years. Race/ethnicity not reported.	States 'fulfilled the current criteria for GnRH analog treatment eligibility' (p. 844). Does not explicitly list what these were. Diagnosis of gender identity disorder at age 16 (p. 843).	B3; P3	Triptorelin at age 13.7 years 3.75 mg q 4 weeks IM. Age 18.6 stopped triptorelin and initiated testosterone-ester mixture.	None reported directly for GnRHa use. At age 35 FSH and LH were elevated owing to gonadectomy	At age 35, all anthropomorphic measurements were within normal limits (50th percentile ± 2 *SD*); fasting labs within normal limits. Patient is 'still convinced that his choice to live as a man was the right one' (p. 846).
De Vries et al. (2011)	Prospective follow-up to compare GD and psychological functioning before and after puberty suppression.	$N = 70$ Mean age = 13.6 (1.8) years Race/ethnicity N\not reported	Not provided in this paper.	Not provided in this paper.	GnRHa, but no drug name given.	AFAB had more anxiety and anger and had more problem behaviors than AMAB. GD was not significantly changed over time.	Both AFAB and AMAB showed significant fewer emotional and behavior problems over time. Both also reported decreases in depressive symptoms and increases in global functioning.
Khatchadourian et al. (2014)	Retrospective chart review; describe patient characteristics, treatment, & response	$N = 84$: 45 AFAB; 37 AMAB 2 undecided natal males Ages 11.4–19.8 years. Race/ethnicity not reported.	Screened by mental health professional. Tanner 2 or +. Diagnosis of gender dysphoria by Utrecht Scale or other scales.	Tanner stage 2	GnRHa 14/15 FtM transitioned to testosterone (7 continued GnRHa, 7 discont. GnRHa). GnRHa to 11 MtF (5 rec'd estrogen and 1		13 months = not pursue change. Drug name not provided.

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
					of these DC'd GnRHa; 1 stopped due to emotional lability; 1 stopped due to heavy smoking. One MtF stopped GnRHa after		
One stopped GnRHa due to mood swings & emotional lability.	Need long-term follow-up studies. FtM patients who undergo mastectomy have more favorable post-op outcomes. Should be told about fertility preservation.						
Klaver et al. (2018)	Retrospective design. Examine how body shape and composition change during treatment with GnRHa	*N* = 192: 71 AMAB 121 AFAB Age 22 years. 3 Asian, 3 Black American, 184 Caucasian (96%)	Diagnosis of gender dysphoria.	Breast stage 2 for girls (age 14.5). Gonad stage 3 for boys (age 15.3)	Sub-q GnRHa 3.75 for 4 weeks. No drug name provided. Added cross-sex hormones at age 16.	Greater changes in body composition (> fat in MtF and < fat in FtM compared to cisgender).	Earlier treatment associated with closer resemblance to desired sex
Nahata et al. (2017)	Retrospective medical record review to examine mental health diagnoses, self-injurious behaviors, school victimization, and rates of insurance for hormone therapy.	*N* = 79: *n* = 28 AMAB *n* = 51 AFAB Ages 9–18 years 83.5% White 6.3% Black 6.3% biracial 2.5% American Indian 1.3% Hispanic	Diagnosis of gender dysphoria and 'readiness' for hormone treatment by psychiatrist (p. 189)	Beginning at Tanner 2–3	27 received GnRHa but no drug name was given.	Cost of GnRHa = up to $25k per year. Only 8 of 27 had insurance coverage	Not reported
Schagen et al. (2016)	Prospective observational study to evaluate efficacy and safety of GnRHa (triptorelin)	*N* = 116: 49 AMAB 67 AFAB Ages 11.1–18.6 years. Race/ethnicity not reported.	Diagnosis of gender identity disorder, lifelong extreme gender dysphoria, psychologically stable, living in supportive environments.	Median Tanner stage at initiation MtF- 4 FtM -	3.75 mg IM Triptorelin (GnRHa) every 4 weeks after initial at 0, 2, 4 week dosing	Decreased alkaline phosphatase - probably related to slowed growth velocity; decrease in lean body mass % and increase in fat %; decreased height velocity.	All subjects had suppressed gonadotropin and sex steroids; testicular volume decreased in MtF and menses ceased in FtM. No sustained creatinine or LFT abnormalities
Schneider et al. (2017)	Longitudinal case report of	*N* = 1 Age 11,	Diagnosis of gender	Tanner stage 2		Global IQ decreased	

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
	effects of puberty suppression on brain white matter.	FMAB. Race/ethnicity not reported.	dysphoria and gender incongruence.		Leuprorelin 3.75 mg. IM/ every 28 days	slightly, some difficulty in math and exact sciences.	Improvement in affective and social life.
Turban et al. (2020)	Cross-sectional survey to relate access to puberty blockers in adolescence and mental health outcomes in adulthood.	*N* = 89 who received puberty blockers between ages 9 and 16. From national Transgender Survey.	Not provided in this paper.	Not provided in this paper.	Not provided in this paper.	None noted	Decreased lifetime suicidal ideation and past-month psychological distress and binge drinking. Reduced lifetime illicit drug use.
Vlot et al. (2017)	Retrospective study of bone turnover markers and bone density in adolescents receiving GnRHa and later HRT	*N* = 70: 28 AMAB 42 AFAB Ages 11.5–18.6. Race/ethnicity not reported.	Diagnosis of gender dysphoria	FtM - start at T2+; MtF - start testicle volume at least 6–8 ml or when T2-3	Triptorelin 3.75 mg subcutaneously every 4 weeks At 16 yo - testosterone or estradiol added.	Decrease in bone turnover markers ICTP and P1NP, also coincides with decrease in BMAD Z scores primarily in lumbar spine (most hormone sensitive); even after HRT started, in most, pretreatment Z scores were not reached even after 24 months on HRT	Some recovery of BMAD Z scores after HRT started

Abbreviations: AFAB, males, assigned female at birth; AMAB, females, assigned male at birth; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist.

Drugs used to suppress puberty

The GnRH analogue drug named to suppress puberty in children in four of the reviewed studies was triptorelin (Cohen-Kettenis et al., 2011; Schagen et al., 2016; Vlot et al., 2017) and leuprorelin (Schneider et al., 2017). The other five studies just used the term GnRHa but provided no specific drug name. Gender-affirming drugs such as testosterone and estradiol were mentioned in some studies as added later in the treatment protocols.

Risks/adverse outcomes

Known risks and adverse outcomes of using GnRHa in children included mood swings and emotional lability (Khatchadourian et al., 2014). Klaver et al. (2018) reported different changes in body composition between patients AMAB and patients AFAB after treatment; persons AMAB had increased fat whereas AFAB persons had decreased fat compared to cisgender peers. Nahata et al. (2017) reported the cost of using GnRHa as an adverse byproduct of this treatment in addition to the lack of insurance coverage. Other adverse risks associated with use of these hormones included slow growth, decrease in lean body mass, increased fat, and decreased height velocity (Schagen et al., 2016); and decrease in bone turnover markers (Vlot et al., 2017).

Positive outcomes associated with GnRHa

Positive outcomes associated with using GnRHa drugs with adolescents included anthropomorphic measurements returning to normal limits in adulthood (Cohen-Kettenis et al. 2011); and better outcomes for patients assigned female at birth who also underwent mastectomy (Khatchadourian et al., 2014). Schagen et al. (2016) reported positive changes in secondary sexual characteristics along with the lack of sustained creatinine or LFT abnormalities. Schneider et al. (2017) reported the individual's improvement in affective and social life. Similarly, de Vries et al. (2011) found

significant improvements in general functioning, decreases in depressive symptoms, and decreases in emotional and behavioral problems. One study reported no positive outcomes (Nahata et al., 2017). Importantly, when compared to youth who did not receive pubertal suppression, those who did showed lower lifetime rates of suicidal ideation (Turban et al., 2020).

Quality

Table 3 is a summary of the quality checklists used to determine quality in the four studies that were retrospective chart reviews. In sum, three of the studies were deemed of fair quality with relatively high risk for bias. These studies had quality scores that were 4 and 5 criteria out of 10 that were met; one study was assessed as good with a score of 7 out of 10 criteria met. The risk of bias in the studies with fair quality was owing to such things as not reporting how data abstractors were trained and monitored, lack of standardized abstraction forms, and lack of procedural manual or description of data abstraction process in the study. None of the studies reviewed here reported having pilot tested the data collection method or tools. All of these studies met the criterion for addressing ethical and legal concerns.

The prospective studies by de Vries et al. (2011), and Schagen et al. (2016), plus the cross-sectional study by Turban et al. (2020), which were assessed using the JBI checklist, earned 'good' ratings as shown in Table 4. The study by Cohen-Kettenis et al. (2011) was a single case study, for which we used the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018), was rated excellent, having met all eight criteria (100%). We also used the JBI Critical Appraisal Checklist for Case Reports for the other single case study by Schneider et al. (2017) and rated it good, with 7 of 8 criteria met (87.5%). The checklists for these two case reports are in Table 5.

Discussion

The studies identified and reviewed here are current with publication dates ranging from 2011 to 2020. As adolescents, their families, and healthcare providers seek more guidance about using GnRHa drugs to suppress puberty, the findings from this critical review are timely, unique, and useful. Given the relatively short amount of time that GnRHa drugs have been used for patients with GD, it is not unexpected that we found no longitudinal empirical studies to guide practice in this expanding population, although studies are currently underway (Olson-Kennedy et al., 2019). At present, the lack of longitudinal data remains a gap in the literature. From an exhaustive search of four databases, however, we were able to answer our four research questions with data from a total sample of $N = 702$ youth described in a mere nine published articles. The samples ranged not only in size (1–192) but also in age (9–35). Although race/ethnicity was reported in <67% of the studies, where it was, the vast majority of participants were Caucasian or White. Clearly, more studies

Table 3. Vassar & Holzmann's quality checklist for retrospective chart reviews of articles in critical review of puberty-blocking drugs (by first author)

Quality Question	Khatchadourian	Klaver	Nahata	Vlot
1. Are there well-defined and clearly articulated research questions?[a]	Aim to describe cohort in hospital Yes = 1	Aim to examine changes and compare Yes = 1	Goals to examine prevalence of mental health diagnoses and insurance coverage. Yes = 1	Objective to investigate course of three bone turnover markers during Rx. Yes = 1
2. Is there clear evidence of an a priori sampling plan?	No = 0	Yes = 1	Yes = 1	Yes = 1
3. Were the variables operationalized adequately?	(e.g., age at first visit, natal sex, Tanner at first visit). Yes = 1	Yes = 1	Yes = 1	Yes = 1
4. Were data abstractors trained and monitored throughout the study?	No = 0	No/not stated = 0	Yes = 1	No = 0
5. Was a standardized abstraction form used?	No/uncertain = 0	No/not stated = 0	Yes = 1	No = 0
6. Was there a procedural manual or description for data abstraction?	No/uncertain = 0	No/not stated = 0	No = 0	No = 0
7. Were there explicit inclusion and exclusion criteria?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
8. Were interrater/intrarater reliability addressed?	No = 0	No = 0	No = 0	No = 0
9. Was there a pilot test of the data collection and analysis?	No/uncertain = 0	No = 0	No = 0	No = 0
10. Were ethical and legal considerations addressed?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
OVERALL ASSESSMENT	Fair: 4/10	Fair: 5/10	Good: 7/10	Fair: 5/10

[a]If there was a clear aim, objective, or goals for the study, and research questions could be inferred, we rated this criterion as 'yes'.

Table 4. Joanna Briggs Institute's critical appraisal checklist for cross-sectional and prospective observational studies

	de Vries et al. (2011)	Schagen et al. (2016)	Turban et al. (2020)
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y
2. Were the study subjects and the setting described in detail?	Y	Y	NA
3. Was the exposure measured in a valid and reliable way?	U	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y
5. Were confounding factors identified?	N	U	Y
6. Were strategies to deal with confounding factors stated?	N	U	Y
7. Were the outcomes measured in a valid and reliable way?	Y	Y	U
8. Was appropriate statistical analysis used?	Y	Y	Y
TOTAL PERCENTS	62.5%	75%	85.7%%

Legend: Y = yes; N = no; U = unclear; NA = not applicable. Denominator does not include items judged 'NA'.

Table 5. Joanna Briggs institute's critical appraisal checklist for case report reports

Criteria	Cohen-Kettenis et al. (2011)	Schneider et al. (2017)
1. Were patient's demographic characteristics clearly described and presented?	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
6. Was the postintervention clinical condition clearly described?	Yes	No
7. Were adverse events (harms) or unanticipated events identified and described	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes
TOTAL criteria met	8/8 = 100%	7/8 = 87.5%

are needed to address the needs of this diverse and expanding population.

Being screened by a mental health professional to establish a diagnosis of gender dysphoria (GD) or gender identity disorder (GID) was found as a prerequisite to using puberty-blocking drugs in half of the studies. The studies that included older samples, meaning that diagnostic prerequisites were met prior to publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), reported using a diagnosis of gender identity disorder (GID) rather than GD. Authors of all the studies reviewed here noted that this diagnosis was an essential starting point before considering the use of puberty suppressors. All studies in this sample also included not initiating puberty suppressing drugs prior to the onset of puberty. These recommendations are consistent with guidelines published by WPATH (2011) and the Endocrine Society (2017), which note that hormonal therapies should not be instituted prior to the onset of puberty. They are also consistent with a gender-affirming conceptualization of care based on the premise that society upholds diversity in gender development and expression (Edwards-Leeper et al., 2016, p 165).

There was general agreement that gonadotropin-releasing hormone analogue (GnRHa) drugs are preferred for puberty suppression. Five of the papers reviewed here described the use of triptorelin or leuprorelin (off-label), followed by sex-affirming hormones. The other four papers did not give the name of the drugs used, but the authors wrote that GnRHa drugs were administered. These procedures follow the 'Dutch protocol' outlined by Delemarre-van de Waal and Cohen-Kettenis (2006) in which 3.75 mg. of triptorelin is given every four weeks intramuscularly or subcutaneously when adolescents have reached Tanner stages 2–3 and have been diagnosed with gender dysphoria (previously gender identity disorder).

As for positive outcomes, improved psychological health was identified in this review (Turban et al., 2020; de Vries et al., 2011). The most recent study by Turban et al. (2020) was the first to demonstrate that access to pubertal suppression during adolescence was associated with decreased lifetime suicidality among transgender adults. In a prospective, longitudinal investigation, de Vries et al. (2011) reported improvements in general functioning as well as decreases in depressive symptoms and emotional and behavioral problems. The findings of these two studies are further supported by a recent longitudinal investigation that found youth aged 9–25 years who engaged in gender-affirming endocrine treatment (i.e., puberty suppression or cross-sex hormones) demonstrated improved mental health over time (Achille et al., 2020). The chance to have more time to consider medical transition was helpful to the young person in one of the case study reports (Cohen-Kettenis et al., 2011). Despite these psychosocial improvements, most of the studies reviewed here focused on biological outcomes rather than psychosocial ones. Although the biological outcomes that affirm the patient's gender are critical to the success of using puberty-blocking drugs, a more holistic view including psychosocial outcomes are equally important to ensure all needs of patients are being met. Such a holistic view highlights both the physical and mental health implications of access to puberty suppression. As the Endocrine Society (2017) indicate, transgender individuals in puberty should be cared for by a multi-disciplinary team that can address both mental and physical health concerns simultaneously.

As other studies have shown, risks and adverse outcomes described in these studies included emotional lability, changes in body composition (e.g., fat deposits), decreased height velocity, decreased bone turnover, decreased bone mineral density, high cost of these drugs, and inadequate insurance coverage. These findings raise issues with important policy implications and beg for further study.

We need more studies that address the potential positive and negative outcomes related to the use of puberty-blocker therapies not only as they affect the individual but also as they affect the family. Families with health insurance policies that do not support all the services described in the WPATH standards of care for transgender adolescents may suffer financial hardships that could be prevented with additional research demonstrating long-term benefits of this treatment (Padula & Baker, 2017). Families may also need counseling and support groups to deal with issues such as stigma, uncertainty about the future (Gray, Sweeney, Randazzo, & Levitt, 2016), grief and family conflict as youth begin to consider seriously pursuing puberty suppression (Ashley, 2019). Research confirms that TGD youth who lack family and other forms of social support bear a heavy burden of psychological distress (McConnell, Birkett, & Mustanski, 2016).

The quality of the studies reviewed was modest but promising. In all the studies reviewed, the primary risk for bias was selection of the samples, but this may be unavoidable given that the population in each case is already self-selected. Nearly half (44%) of the studies reviewed were retrospective chart reviews and only one of these was rated as 'good', which meant that it had a relatively low risk for bias compared to the others. Because the other three studies omitted important criteria for retrospective chart reviews, they reflected fairly large risks for bias, particularly concerning the inexact methods by which data were extracted from the patients' records. Although the remaining studies were deemed 'good' or 'excellent' in terms of meeting more criteria for their respective study designs, these designs provided low-level evidence: case reports, prospective observational, and cross-sectional studies. Case studies are considered to be the weakest of designs or lowest form of evidence, containing threats to internal validity including history, maturation, and mortality (Campbell & Stanley, 1963; Cochrane, n.d.). These findings suggest the need for additional studies to be conducted using more rigorous designs with fewer threats to internal validity.

The findings from this review support the position taken by Reisner et al. (2016) that we need more longitudinal studies on youth who have taken puberty-blocking drugs in adolescence. Such studies as well as studies using mixed methods designs could document both biological and psychosocial changes over time and are able to provide a more holistic and comprehensive view of how the use of such agents affects the lives of individuals as they explore this critical time of development. Moreover, qualitative studies are needed to document the first-person experiences of TGD youth, as Vrouenraets et al. (2016) have also suggested.

Additional research can lend more strength to current clinical guidelines and assist clinicians in caring for these patients and their families especially as questions arise during treatment. Underscoring the need for ongoing research, access to puberty blockers, and the potential benefits that they provide, is not universal and varies greatly by geography, insurance status, healthcare provider availability among other factors (Kimberly et al., 2018). An increase in high-quality longitudinal data should lend additional support to what healthcare providers are witnessing clinically: improvements in short- and long-term health outcomes of these very vulnerable youth. With additional research should come increased access to these treatment modalities and improvements in mental health outcomes.

Limitations

This study was limited to a review of papers published in English, thus we may have missed important findings published in other languages and other countries. This study was also limited to only four databases. Other databases may have included studies that we missed. Our specific research questions also may have limited our inclusion criteria. Despite these limitations, the findings are strengthened by our adherence to a critical and systematic review process, including the extensive search assistance from an experienced science librarian (last author), and the relatively large number of total participants in the nine studies reviewed.

Implications

The implications for multidisciplinary teams of healthcare professionals working with this population are that this body of research supports the use of puberty suppression in early adolescents who are carefully screened for gender dysphoria and who have reached an early stage of pubertal development.

Conclusion

Despite a recent increase in the number of TGD youth seeking healthcare services for their gender dysphoria, there exists a relatively small amount of research regarding the positive and negative short- and long-term effects of using GnRHa drugs to suppress puberty and to allow more time for gender identity exploration. The need for additional well-designed longitudinal and mixed methods studies is critical to support and even improve current practice for this very vulnerable population. Although large long-term studies with diverse and multicultural populations have not been done, the evidence to date supports the finding of few serious adverse outcomes and several potential positive outcomes. This literature suggests the need for TGD youth to be cared for in a manner that not only affirms their gender identities but that also minimizes the negative physical and psychosocial outcomes that could be associated with pubertal development.

Acknowledgements

There was no funding source for this study. The authors have declared that they have no competing or potential conflicts of interest.

Ethical approval

No ethical approval was required for this review article.

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Manuscript received 2 June 2020; In revised form 8 October 2020;

Accepted for publication: 18 November 2020

HHS Public Access

Author manuscript

Pediatrics. Author manuscript; available in PMC 2020 March 15.

Published in final edited form as:

Pediatrics. 2020 February ; 145(2): . doi:10.1542/peds.2019-1725.

Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation

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Abstract

BACKGROUND AND OBJECTIVES: Gonadotropin-releasing hormone analogues are commonly prescribed to suppress endogenous puberty for transgender adolescents. There are limited data regarding the mental health benefits of this treatment. Our objective for this study was to examine associations between access to pubertal suppression during adolescence and adult mental health outcomes.

METHODS: Using a cross-sectional survey of 20 619 transgender adults aged 18 to 36 years, we examined self-reported history of pubertal suppression during adolescence. Using multivariable logistic regression, we examined associations between access to pubertal suppression and adult mental health outcomes, including multiple measures of suicidality.

RESULTS: Of the sample, 16.9% reported that they ever wanted pubertal suppression as part of their gender-related care. Their mean age was 23.4 years, and 45.2% were assigned male sex at birth. Of them, 2.5% received pubertal suppression. After adjustment for demographic variables and level of family support for gender identity, those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2–0.6).

CONCLUSIONS: This is the first study in which associations between access to pubertal suppression and suicidality are examined. There is a significant inverse association between

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Dr Turban conceptualized and designed the study, drafted the initial manuscript, and incorporated all revisions and comments; Ms King conducted statistical analyses and reviewed and revised the manuscript for important intellectual content, with a focus on statistical aspects of the manuscript; Dr Carswell assisted in the design of the study and in interpretation of the data analyses and critically reviewed and revised the manuscript for important intellectual content, with a focus on relevant clinical endocrinology; Dr Keuroghlian supervised and contributed to the conceptualization and design of the study and the design of the statistical analyses and reviewed and revised the manuscript for important intellectual content as it relates to mental health considerations for transgender people; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

POTENTIAL CONFLICT OF INTEREST: Dr Turban reports receiving royalties from Springer for a textbook on pediatric gender identity; and Ms King and Drs Carswell and Keuroghlian have indicated they have no potential conflicts of interest to disclose.

treatment with pubertal suppression during adolescence and lifetime suicidal ideation among transgender adults who ever wanted this treatment. These results align with past literature, suggesting that pubertal suppression for transgender adolescents who want this treatment is associated with favorable mental health outcomes.

According to the Centers for Disease Control and Prevention's Youth Risk Behavior Surveillance System, ~1.8% of adolescents in the United States identify as transgender.[1] These youth suffer mental health disparities that include higher rates of internalizing psychopathology (ie, anxiety and depression) and suicidality, theorized to be due to a combination of dysphoria toward their bodies and minority stress.[2–5] In a large study of transgender adults in the United States, 40% endorsed a lifetime suicide attempt.[6]

Over the past 2 decades, protocols have been developed to provide transgender adolescents with gender-affirming medical interventions that align their bodies with their gender identities. Most prominent among these are the Endocrine Society guidelines[7] and the World Professional Association for Transgender Health (WPATH) Standards of Care.[8] Both sets of guidelines recommend that transgender adolescents be offered gonadotropin-releasing hormone analogues (GnRHas), colloquially referred to as "puberty blockers," once they reach Tanner 2 of puberty. These medications are provided as subcutaneous implants or are administered as either 1- or 3-month depot injections. GnRHa therapy effectively halts the production of gonadal sex steroids (testosterone and estrogen) by persistently activating and thereby desensitizing the gonadotropin-releasing hormone receptor, which in turn leads to suppression of luteinizing hormone and follicle-stimulating hormone release from the anterior pituitary gland.[9] This process inhibits endogenous puberty for the duration of GnRHa use. Once further pubertal development is delayed, youth are able to explore gender identities without the pressure of dysphoria associated with gender-incongruent physical development.[10] GnRHa therapy is unique among gender-affirming medical interventions in that the resultant pubertal suppression is fully reversible, with the resumption of endogenous puberty after their discontinuation.[7,8]

Since the publication of the WPATH Standards of Care and the Endocrine Society guidelines, the use of pubertal suppression for transgender youth has become more common in the United States[9] There are limited data, however, regarding the mental health outcomes of pubertal suppression. To date, there have been 2 published studies in which the effects of this treatment on the mental health of transgender youth were examined. In the first study, the authors assessed changes in mental health among 55 Dutch adolescents who received pubertal suppression.[11] This study, which notably lacked a control group, revealed that internalizing psychopathology improved after treatment with pubertal suppression. In the second study, researchers followed a group of 201 adolescents with gender dysphoria and found that those who received pubertal suppression in addition to psychological support (n = 101) had superior global functioning, measured by the Children's Global Assessment Scale, when compared with those who received psychological support alone (n = 100).[12]

In the current study, we use the largest survey of transgender people to date, a community-recruited sample of transgender adults in the United States, to conduct the first-ever investigation into associations between pubertal suppression and suicidality.

Transgender youth present to clinicians with a range of concerns. Some have minimal body dysphoria and do not desire pubertal suppression, whereas others report significant dysphoria around the physical changes related to puberty. Because not all transgender and gender-diverse youth desire medical interventions, we examined only those youth who desired pubertal suppression because these are the young people who would present to care and for whom clinicians would need to decide about whether to initiate pubertal suppression. We specifically examined measures of past-year suicidality, lifetime suicidality, past-month severe psychological distress, past-month binge drinking, and lifetime illicit drug use. We hypothesized that among those who wanted pubertal suppression, those who received it would have superior mental health outcomes when compared with those who wanted but did not receive it.

METHODS

Study Design and Data Source

The 2015 US Transgender Survey (USTS) was conducted over a 1-month period in 2015 by the National Center for Transgender Equality (NCTE). It is, to our knowledge, the largest existing data set of transgender adults and includes data regarding demographics, past gender-affirming medical treatment, family support, and mental health outcomes. Participants were recruited through community outreach in collaboration with >400 lesbian, gay, bisexual, and transgender organizations and were provided with a Web address to complete the survey online. Details regarding outreach efforts are further described in the NCTE report on the survey.[6] The USTS protocol was approved by the University of California, Los Angeles Institutional Review Board. For the purposes of the current study, data were obtained via a data-sharing agreement with the NCTE, and the current protocol was reviewed by The Fenway Institute Institutional Review Board and determined to not comprise human subjects research.

Study Population

The USTS data set contains responses from 27 715 US transgender adults, with respondents from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. Given that pubertal suppression for transgender youth was not available in the United States until 1998,[4] only participants who were 17 or younger in 1998 would have had health care access to GnRHa for pubertal suppression. We thus restricted the analysis to participants who were 36 or younger at the time of the survey, resulting in a sample of 20 619 participants. Data were further restricted to those who selected “puberty blocking hormones (usually used by youth ages 9–16)” in response to the question “Have you ever wanted any of the health care listed below for your gender identity or gender transition? (Mark all that apply).” Response options for this question were “counseling/therapy,” “hormone treatment/HRT,” “puberty blocking hormones (usually used by youth ages 9–16),” or “none of the above.” This resulted in a sample of 3494 individuals between the ages of 18 and 36 who ever wanted pubertal suppression as part of their gender-affirming medical care.

Exposures

Exposure to pubertal suppression was defined as selecting "puberty blocking hormones (usually used by youth ages 9–16)" in response to the question "Have you ever had any of the health care listed below for your gender identity or gender transition? (Mark all that apply)." Response options for this question were "counseling/therapy," "hormone treatment/HRT," "puberty blocking hormones (usually used by youth ages 9–16)," and "none of the above." Participants who reported having pubertal suppression were also asked, "At what age did you begin taking Puberty Blocking Hormones?" Those who reported beginning treatment after age 17 were excluded to only include participants who likely had pubertal suppression during active endogenous puberty. The vast majority of adolescents would have reached Tanner 5, the final stage of puberty, by age 17.[13,14]

Outcomes

Comparing those who received pubertal suppression with those who did not, we examined past-month severe psychological distress (defined as a score of ≥13 on the Kessler Psychological Distress Scale [K6], a cutoff previously validated among US adults[15]), past-month binge drinking (operationalized as drinking ≥5 standard alcoholic beverages during 1 occasion; the rationale for this threshold when studying alcohol use among transgender people has been discussed previously[16]), lifetime illicit drug use (not including marijuana), past-year suicidal ideation, past-year suicidal ideation with a plan, past-year suicide attempts, past-year suicide attempts resulting in inpatient care, lifetime suicidal ideation, and lifetime suicide attempts.

Control Variables

Demographic variables collected included age, age of social transition, age of initiation of gender-affirming hormone therapy, current gender identity, sex assigned at birth, sexual orientation, race, education level, employment status, relationship status, total household income at the time of data collection in 2015, family support for gender identity, and current hormone treatment.

Statistical Analysis

Data were analyzed by using SPSS software version 25 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Descriptive statistics were conducted and are presented as frequency (percentage) or mean (SD). Analysis of variance and χ^2 tests were used to assess significance by age, gender identity, sex assigned at birth, race, education level, employment status, relationship status, total household income, family support for gender identity, and current hormone treatment between those who received pubertal suppression and those who did not. We used univariate logistic regression to examine associations between receiving pubertal suppression and each mental health outcome, as well as between age and both ever wanting and receiving pubertal suppression. $P < .05$ defined statistical significance. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with level of family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide

attempts were associated with gender identity, and this model was therefore additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and therefore models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts; therefore models were therefore additionally adjusted for race.

RESULTS

Of the 20 619 survey respondents 18 to 36 years of age, 3494 (16.9%) reported that they had ever wanted pubertal suppression. Of those who wanted pubertal suppression, only 89 (2.5%) had received this treatment. The following variables were found to be associated with those who wanted and received pubertal suppression compared with those who wanted pubertal suppression but did not receive it: younger age, age of social transition, age of initiation of hormone therapy, feminine gender identity, male sex assigned at birth, heterosexual sexual orientation, higher total household income, and greater family support of gender identity (Table 1).

In univariate analyses, when comparing those who received pubertal suppression with those who did not, receiving pubertal suppression was associated with decreased odds of past-year suicidal ideation, lifetime suicidal ideation, and past-month severe psychological distress (Table 2). After controlling for demographic variables from Table 1, pubertal suppression was associated with decreased odds of lifetime suicidal ideation. Raw frequency outcomes are presented in Table 3.

To examine associations between age, ever wanting, and ever receiving pubertal suppression, we divided participants into 2 age groups with the cutoff point at the median, 18 to 22 and 23 to 36, in light of the skewed distribution of age.[17] The younger age group had increased odds both of ever wanting pubertal suppression (odds ratio [OR] = 1.4, $P < .001$, 95% confidence interval [CI]: 1.3–3.5) and of receiving pubertal suppression (OR = 2.1, $P = .001$, 95% CI: 1.4–3.4).

Among those who had ever received pubertal suppression, 60% reported traveling, 25 miles for gender-affirming health care, 29% traveled between 25 and 100 miles, and 11% traveled .100 miles.

DISCUSSION

This study is the first in which the association between access to pubertal suppression and measures of suicidality is examined. Treatment with pubertal suppression among those who wanted it was associated with lower odds of lifetime suicidal ideation when compared with those who wanted pubertal suppression but did not receive it. Suicidality is of particular concern for this population because the estimated lifetime prevalence of suicide attempts among transgender people is as high as 40%.[6] Approximately 9 of 10 transgender adults who wanted pubertal suppression but did not receive it endorsed lifetime suicidal ideation in the current study (Table 3). Access to pubertal suppression was associated with male sex

assignment at birth, heterosexual sexual orientation, higher total household income, and higher level of family support for gender identity.

Results from this study suggest that the majority of transgender adults in the United States who have wanted pubertal suppression did not receive it. Of surveyed transgender adults in the current study, 16.9% reported ever desiring pubertal suppression as part of their gender-related care; however, only 2.5% of these respondents indicated they had in fact received this wanted treatment. This was the case even for the youngest survey respondents, who were 18 years old at the time of data collection in 2015. Only 4.7% of 18-year-olds who wanted the treatment reported receiving it.

Although rates both of desiring and of receiving pubertal suppression were higher among younger respondents, results from the current study indicate that still only 29.2% of the youngest participants in the study (ie, those who were 18 years of age in the year 2015) reported ever desiring pubertal suppression as part of gender-related care. No individuals <18 years of age were captured by this data set; future research should investigate the rate of desiring pubertal suppression among younger populations. Some respondents may have simply never been aware of the possibility of puberty suppression while still within the range of developmentally suitable candidates for receiving this treatment, or they may have believed that they were not suitable candidates. This finding may also reflect the diversity of experience among transgender and gender-diverse people, highlighting that not all will want every type of gender-affirming intervention.[7,8] Future research is needed to understand why younger participants reported desiring pubertal suppression at higher rates; we hypothesize that this is likely due in part to recent increased public awareness about and access to gender-affirming interventions.[5]

Access to pubertal suppression was associated with a greater total household income. Without insurance, the annual cost of GnRHa therapy ranges from $4000 to $25 000.[18] Among adolescents treated with pubertal suppression at the Boston Children's Hospital Gender Management Service before 2012, <20% obtained insurance coverage.[19] More recently, insurance coverage for these medications has increased: a study from 2 academic medical centers in 2015 revealed that insurance covered the cost of GnRHa therapy in 72% of cases.[18] This is 1 potential explanation for why younger age was found to be associated with accessing pubertal suppression in the current study (Table 1). It is also plausible that those who receive pubertal suppression experience more improvement in mental health, which in turn may contribute to greater socioeconomic advancement.[20] This study's cross-sectional design limits further interpretation.

Participants who endorsed a heterosexual sexual orientation were more likely to have received pubertal suppression. This is in line with past research revealing that nonheterosexual transgender people are less likely to access gender-affirming surgical interventions.[21] Some clinicians may be biased against administering pubertal suppression to patients whose sexual orientation identities do not align with society's heteronormative assumptions.[21] In the current study, nonbinary and genderqueer respondents were also less likely to have accessed pubertal suppression, suggesting that clinicians may additionally be uncomfortable with delivering this treatment to patients whose gender identities defy more

traditional binary categorization. Of note, because research on gender-affirming hormonal interventions for adolescents has been focused on transgender youth with binary gender identities,[11] some clinicians have reservations about prescribing pubertal suppression interventions to nonbinary youth in the event of a potentially prolonged state of low sex-steroid milieu.

Family support was also associated with receiving pubertal suppression among those who wanted this treatment. This finding is unsurprising given that most states require parental consent for adolescents to receive pubertal suppression.[22] Past studies have revealed that family support of gender identity is associated with favorable mental health outcomes.[6] Of note, treatment with pubertal suppression in the current study was associated with lower odds of lifetime suicidal ideation, even after adjustment for family support (Table 2).

We did not detect a difference in the odds of lifetime or past-year suicide attempts or attempts resulting in hospitalization. It is possible that we were underpowered to detect these differences given that suicide attempt items were less frequently endorsed than suicidal ideation items (Table 3). Given this study's retrospective self-report survey design, we were unable to capture information regarding completed suicides, which may have also reduced the number of suicide attempts we were able to account for. Given that suicidal ideation alone is a known predictor of future suicide attempts and deaths from suicide, the current results warrant particular concern.[23]

This study adds to the existing literature[11,12] on the relationship of pubertal suppression to favorable mental health outcomes. The theoretical basis for these improved mental health outcomes is that pubertal suppression prevents irreversible, gender-noncongruent changes that result from endogenous puberty (eg, bone structure, voice changes, breast development, and body hair growth) and that may cause significant distress among transgender youth. Pubertal suppression allows these adolescents more time to decide if they wish to either induce exogenous gender-congruent puberty or allow endogenous puberty to progress.[7,8] Some have also theorized that gender-affirming medical care may have mental health benefits that are separate from its physical effects because it provides implied affirmation of gender identity from clinicians, which may in turn buffer against minority stress.[24]

Strengths of this study include its large sample size and representation of a broad geographic area of the United States. It is the first study in which associations between pubertal suppression for transgender youth and suicidality are examined. Limitations include the study's cross-sectional design, which does not allow for determination of causation. Longitudinal clinical trials are needed to better understand the efficacy of pubertal suppression. Because the 2015 USTS data do not contain the relevant variables, we were unable to examine associations between access to pubertal suppression and degree of body dysphoria in this study. Notably, past studies have revealed that body image difficulties persist through pubertal suppression and remit only after administration of gender-affirming hormone therapy with estrogen or testosterone.[11] It is also limited by its nonprobability sample design. Future researchers should work toward the collection of population-based survey data that include variables related to gender-affirming medical interventions. Of note, because pubertal suppression for transgender youth is a relatively recent intervention, some

participants might not have known that these interventions existed and thus would not have reported ever wanting them. Had these individuals known about pubertal suppression, it is possible that they might have desired it. Because we do not have data on whether individuals who did not desire pubertal suppression would have wanted it had they known about it, we restricted our analysis to those who reported ever desiring pubertal suppression. Reverse causation cannot be ruled out: it is plausible that those without suicidal ideation had better mental health when seeking care and thus were more likely to be considered eligible for pubertal suppression. The Endocrine Society guidelines for pubertal suppression eligibility recommend that other mental health concerns be "reasonably well controlled."[7] Because this study includes only adults who identify as transgender, it does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender. Notably, however, a recent study from the Netherlands of 812 adolescents with gender dysphoria revealed that only 1.9% of adolescents who initiated pubertal suppression discontinued this treatment without proceeding to gender-affirming hormone therapy with estrogen or testosterone.[25]

CONCLUSIONS

Among transgender adults in the United States who have wanted pubertal suppression, access to this treatment is associated with lower odds of lifetime suicidal ideation. This study strengthens recommendations by the Endocrine Society and WPATH for this treatment to be made available for transgender adolescents who want it.

ACKNOWLEDGMENT

We thank the NCTE for conducing the 2015 USTS and for allowing us access to these data.

FUNDING: Supported by grant U30CS22742 from the Health Resources and Services Administration Bureau of Primary Health Care to Dr Keuroghlian, the principal investigator, by contract AD-2017C1-6271 from the Patient-Centered Outcomes Research Institute to Dr Kenneth H. Mayer, the principal investigator (Dr Keuroghlian is co-investigator), and by a Pilot Research Award for General Psychiatry Residents from The American Academy of Child & Adolescent Psychiatry to Dr Turban.

ABBREVIATIONS

CI	confidence interval
GnRHa	gonadotropin-releasing hormone analogue
K6	Kessler Psychological Distress Scale
NCTE	National Center for Transgender Equality
OR	odds ratio
USTS	US Transgender Survey
WPATH	World Professional Association for Transgender Health

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WHAT'S KNOWN ON THIS SUBJECT:

Gonadotropin-releasing hormone analogues are commonly used to suppress endogenous puberty for transgender adolescents. Small studies have revealed that pubertal suppression results in favorable mental health outcomes. No studies to date have examined associations between pubertal suppression and suicidality.

WHAT THIS STUDY ADDS:

In this study, using the largest survey of transgender adults to date, we show that access to pubertal suppression during adolescence is associated with lower odds of lifetime suicidal ideation among transgender young adults.

TABLE 1

Sample Demographics

		Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?			
	All (*N* = 3494)	**Yes (*n* = 89; 2.5%)**	**No (*n* = 3405; 97.5%)**	**F**	***P***
n (%)*n* (%)*n* (%)					
Age	23.4 (5.0)	21.7 (4.7)	23.4 (5.0)	10.3	.001 *
Age of social transition	20.0 (5.5)	15.2 (4.5)	20.1 (5.5)	67.5	<.001 *
Age began hormone therapy	22.1 (4.5)	15.7 (2.4)	22.5 (4.3)	217.4	<.001 *
Gender identity				25.5[a]	<.001 *
Woman		23 (25.8)	617 (18.2)		
Man		19 (21.3)	383 (11.3)		
Transgender woman		25 (28.1)	720 (21.3)		
Transgender man		16 (18.0)	795 (23.5)		
Nonbinary or genderqueer		6 (6.7)	866 (25.6)		
Sex assigned at birth				4.4[a]	.04 *
Female		39 (43.8)	1874 (55.0)		
Male		50 (56.2)	1531 (45.0)		
Sexual orientation				36.5[a]	<.001 *
Heterosexual or straight		27 (30.3)	350 (10.3)		
Asexual		9 (10.1)	437 (12.8)		
Pansexual or queer		36 (40.4)	1784 (52.4)		
Gay or lesbian		12 (13.5)	539 (15.8)		
Not listed		5 (5.6)	295 (8.7)		
Race, *n* (%)				3.5[a]	.06
Racial minority		28 (31.5)	782 (23.0)		
Not racial minority (white or European American)		61 (68.5)	2623 (77.0)		
Education level				2.9[a]	.41
Less than high school		9 (10.1)	220 (6.5)		
High school graduate or GED		20 (22.5)	683 (20.1)		

		Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?			
	All (*N* = 3494)	**Yes (*n* = 89; 2.5%)**	**No (*n* = 3405; 97.5%)**	**F**	***P***
Some college or associate degree		39 (43.8)	1729 (50.8)		
Bachelor's degree or higher		21 (23.6)	773 (22.7)		
Employment status				0.6[a]	.45
Employed		51 (79.7)	1976 (75.6)		
Unemployed		13 (20.3)	638 (24.4)		
Relationship status				0.5[a]	.47
Partnered		35 (40.2)	1447 (44.1)		
Unpartnered		52 (59.8)	1834 (55.9)		
Total household income, $				21.9[a]	<.001*
<25 000		21 (26.3)	1153 (38.3)		
25 000–49 999		13 (16.3)	652 (21.7)		
50 000–99 000		14 (17.5)	630 (20.9)		
>100 000		32 (40.0)	574 (19.1)		
Family support for gender identity					
Supportive		71 (81.6)	1551 (55.8)	24.3[a]	<.001*
Neutral		11 (12.6)	573 (20.6)		
Unsupportive		5 (5.7)	658 (23.7)		
Current hormone treatment		87 (97.8)	1617 (96.3)	0.5[a]	.48

Descriptive statistics for transgender adults in the United States who ever wanted pubertal suppression for their gender identity or gender transition when comparing those who received this treatment with those who did not receive this treatment (total $N = 3494$). Percentages were calculated from the total of nonmissing values.

*Indicates statistical significance.

[a]χ^2.

TABLE 2

Mental Health Outcomes Among Those Who Received Pubertal Suppression

	Univariate Analyses		Multivariable Analyses	
	OR (95% CI)	***P***	**aOR (95% CI)**	***P***
Suicidality, past 12 mo				
Ideation	0.6 (0.4–0.8)	.006*	0.6 (0.3–1.1)	0.09
Ideation with plan	0.9 (0.5–1.6)	.73		
Ideation with plan and attempt	1.2 (0.6–2.3)	.64		
Attempt resulting in inpatient care	2.8 (0.8–9.4)	.09		
Suicidality, lifetime				
Ideation	0.3 (0.2–0.5)	<.001*	0.3 (0.2–0.6)	0.001*
Attempts	0.7 (0.4–1.0)	.08		
Mental health and substance use				
Past-month severe psychological distress, K6 ≥13	0.5 (0.3–0.8)	.001*	0.8 (0.4–1.4)	0.38
Past-month binge drinking	0.3 (0.8–2.0)	.29		
Lifetime illicit drug use	1.1 (0.7–1.8)	.67		

Univariate and multivariable analyses of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression when comparing those who received this treatment with those who did not. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide attempts were associated with gender identity, and this model was additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and thus these models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts, and thus these models were additionally adjusted for race. Models for psychological distress and past-year suicidal ideation were also adjusted for age, gender identity, and relationship status. aOR, adjusted odds ratio.

[a]Indicates statistical significance.

TABLE 3

Raw Frequencies of Outcome Variables

	Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?	
	Yes (*n* = 89; 2.5%)	No (*n* = 3405; 97.5%)
	n (%)	*n* (%)
Suicidality (past 12 mo)		
Ideation	45 (50.6)	2204 (64.8)
Ideation with plan	25 (55.6)	1281 (58.2)
Ideation with plan and attempt	11 (24.4)	473 (21.5)
Attempt resulting in inpatient care	5 (45.5)	108 (22.8)
Suicidality (lifetime)		
Ideation	67 (75.3)	3062 (90.2)
Attempts	37 (41.6)	1738 (51.2)
Mental health and substance use		
Past-month severe psychological distress (K6 ≥13)	32 (37.2)	1847 (55.1)
Past-month binge drinking	26 (29.2)	825 (24.3)
Lifetime illicit drug use	24 (27.3)	850 (25.3)

Raw frequencies of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression. Percentages were calculated from the total of nonmissing values.