A PARADIGM SHIFT IN THE TREATMENT OF HIGH-RISK SUBSTANCE USE AND OVERDOSE AMONG YOUTH

by

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A Paradigm Shift in the Treatment of High-Risk Substance Use and Overdose Among Youth

submitted by	Jean Nicolas Westenberg	in partial fulfillment of the requirements for
the degree of	Master of Science	
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Abstract

Mental and substance use disorders are the leading cause of disability and overall burden of disease in children and youth worldwide. Further, overdose and suicide are the leading contributors to mortality among youth in North America. The need for effective healthcare systems for youth will only become more substantial, especially in the context of the opioid overdose crisis and the COVID-19 pandemic. This research investigated the current paradigm surrounding substance use disorder treatment among youth and aimed to contribute a more innovative and effective response to high-risk substance use and overdose among youth. Firstly, a narrative review assessed the current reality of treatment approaches for high-risk opioid use among youth by means of narrative review. Findings revealed a dearth of academic effort and clinical research on interventions for youth with high-risk substance use, which demonstrates the many gaps within the field of addiction psychiatry and adolescent medicine. Secondly, a rapid review evaluated the clinical guidance in place for youth with high-risk opioid use. The clinical practice guidelines available, or lack thereof, reaffirms the systematic failure in addressing the mental health and substance use needs of youth. Lastly, to inform service development and ameliorate the standard of care for youth, a multidisciplinary panel of clinicians and researchers in the field of youth substance use disorder developed 60 recognized statements through Delphi process. This international collaborative project provides a basis for education and establishes an infrastructure for research by outlining clinical risks, determining target populations, defining intervention goals, recognizing evidence-based strategies, and identifying appropriate treatment settings and expertise. Comprehensively, this research identifies critical problems in the current systems of care for adolescents and young adults internationally and provides a framework for the improved prevention, treatment, and management of high-risk substance use and overdose among this vulnerable group. Healthcare systems must strive to support youth through their development with tailored and stigma-free evidence-based approaches. High-quality studies are needed to further determine the safety and effectiveness of treatment options for youth.

Lay Summary

Of obvious public-health significance is the enhanced risk of premature death that is associated with mental and substance use disorders among adolescents and young adults. The need for effective service systems for youth will only become more substantial, especially in the context of the opioid overdose crisis and the COVID-19 pandemic. This research aimed to shift the current paradigm surrounding high-risk substance use and overdose among youth. A review of the literature demonstrated a lack of academic efforts in this domain, and a review of clinical guidance revealed major gaps between policy, research and clinical practice. Consensus among international experts was created to address the dysfunctional treatment system for youth and the fragmented current state of research and clinical care. This research identifies critical problems in the current system of care and provides a framework to address the prevention, treatment, and management of high-risk substance use and overdose among youth.

Preface

This statement is to confirm that the work presented in this dissertation was conceived, conducted, analyzed, and written by the candidate, Jean Nicolas Westenberg, with guidance from Dr. R. Michael Krausz (Supervisor), Dr. Christian G. Schütz (Supervisory Committee Member), and Dr. Nickie Mathew (Supervisory Committee Member).

Sections within Chapter 1 (1.1.3, 1.1.4, 1.1.5, 1.2) have been published in two articles. The first was an opinion piece submitted by invitation: Westenberg JN, Wong JSH, Krausz RM. The urgent need for an interdisciplinary approach to pediatric mental health and addiction. *World Child Adolesc Psychiatry*. 2020;(19):18-21. The second was a timely perspective article: Krausz RM, Wong JSH, Westenberg JN, Choi F, Schütz CG, Jang KL. Canada's Response to the Dual Public Health Crises: A Cautionary Tale. *Can J Psychiatry*. 2021. doi:10.1177/0706743721993634. Since both publications are opinion articles, they required no collection or interpretation of data. I was involved in the design and writing of both manuscripts.

A version of Chapter 2 has been published. Westenberg JN, Tai AMY, Elsner J, et al. Treatment approaches and outcome trajectories for youth with high-risk opioid use: A narrative review. *Early Interv Psychiatry*. April 2021:1-14. doi:10.1111/eip.13155. I was part of study design, data collection, data analysis and interpretation, and in the writing of the manuscript, along with Andy Tai, Julie Elsner, Mostafa Kamel, James Wong and with support from Dr. R. Michael Krausz.

The content in Chapter 3 has not been submitted or been published anywhere. The data presented in it was collected by members of the Addiction and Concurrent Disorders (ACD) research team (Janet Suen, Kimia Ziafat, Andy Tai). As a member of the ACD research team, I was part of design, data collection, data cleaning, data analysis and interpretation. I was the lead investigator, responsible for writing and preparing the manuscript, supported by Dr. R Michael Krausz and members of the ACD research team.

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List of Abbreviations

ADHD: Attention-deficit/hyperactivity disorder BC: British Columbia HCV: Hepatitis C virus HIV: Human immunodeficiency virus MDD: Major depressive disorder OAT: Opioid agonist treatment OUD: Opioid use disorder PTSD: post-traumatic stress disorder PWID: people who inject drugs PWUD: people who use drugs RCT: randomized controlled trial

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Dedication

It is a fact that every individual living in the world today is either currently a kid or once was a kid. Why does adult society therefore undertake a special form of self-harm by continuing to neglect child and adolescent psychiatry?

To all the children, adolescents, and young adults who have died from overdose and suicide in Canada in the last decade, who deserved much more care and support and who were robbed of the opportunity to chase their dreams and meet their human potential.

1. Background, rationale, and objectives

1.1. Background

1.1.1. Adolescence and young adulthood: a period of change

The term "youth" is broadly understood as the developmental period which begins with changes of puberty and culminates in the assumption of adult roles (1). There are varied definitions that exist for this period, but the World Health Organization (WHO) defines a young person as an individual between 10 and 24 years old, which includes adolescence and young adulthood (2). It can be conceptualized as a developmental period rather than a temporal snapshot. It is a sensitive period characterized by significant developmental changes across all domains (3). Biologically, puberty brings on a constellation of major physical alterations: sexual maturation, changes in body composition, and rapid skeletal growth (4,5). This also coincides with changes in an individual's social and familial environment (6). Individuals are usually inclined to spend less time with parents while spending more with peers as they strive to become more autonomous and independent.

These large-scale developments are influenced by external environmental factors such as family, peers, schools, communities, and media, as well as by internal factors including brain structure and connectivity, that elicit and reinforce behaviours (7–10). For instance, the risk of substance use escalates during mid-to-late adolescence, particularly due to an individual's exposure to new peers, who may provide access to licit and illicit drugs, and due to neural developmental imbalances in the brain pathways underlying pleasure seeking and decision-making (11–13) However, experimenting with substances may also fulfil the normal developmental drives characteristic of adolescences and young adulthood (1,14). Adolescence is a delicate stage of life during which individuals develop their identity by rethinking who they are and want to be, a process called identity formation (15). This key developmental task in adolescence happens through exploration, in which youth sort through various identity elements in an attempt to determine a set of goals, values, and beliefs that will sustain them through the transition to adulthood and beyond (16–19). In line with this, experimenting and risk-taking during adolescence is likely to be normative, biologically driven and, to a certain extent, inevitable (20,21).

As youth grow and reach their developmental competencies, the external environmental they are exposed to, as well as the internal characteristics they explore and develop, can increase or decrease their likelihood of experiencing adverse outcomes and developing mental and substance use disorders (22). Risk factors such as adverse or traumatic childhood experiences, perceived rejection from parents or caring adults, familial histories of mental and substance use disorders, social and academic impairment, are associated with detrimental mental health (23–26). Protective factors such as pronounced individual, family and social resources, supportive family, school, and community environments, opportunities for engagement with school and community, physical and psychological safety, high self-esteem, good resilience and coping skills, have been shown to be associated with a reduced occurrence of mental health problems, especially in children with a limited number of risk factors (23–25). Many factors can therefore protect or expose an individual to developing a mental and/or substance use disorder. Due to the unique developmental milestones of youth, limiting the risk factors and strengthening the protective factors is critical to their positive development, and requires relevant and appropriate support to meet their complex needs (27).

1.1.2. Disability and burden of disease

Unfortunately, mental and substance use disorders are the leading cause of disability in children and youth worldwide, equivalent to roughly a quarter of all years lived with disability in children and youth (54.2 million) (28,29). This represents a serious international challenge. In high income countries (HIC), mental and substance use disorders are the leading cause of overall burden of disease in children and youth, equivalent to roughly one fifth of the total burden of disease in children and youth (Figure 1.1) (28). For example, in Australia, suicide and self-inflicted injuries, anxiety disorders, and depressive disorders were the first, second and third leading causes of burden in young people aged 15–24 respectively (Figure 1.2) (30). Though similar data on disability and burden of disease among youth within Canada and the United States is not available, overdose and suicide represent the leading causes of death among adolescents and young adults in both countries (31,32). In low- and middle-income countries (LMIC), a large proportion of burden of disease in children and youth is accounted for by infectious diseases and neonatal disorders, but these are gradually being addressed through vaccination efforts, accessibility to treatment, better nutrition and sanitation, etc. (28). As this

trend continues, the need for effective service systems for youth mental health will only become more substantial in LMIC. Moreover, healthcare systems in HIC will need to devote more resources to children and youth with mental and substance use disorders to build and/or update functional treatment approaches for youth. This is especially true in the context of the opioid overdose crisis and the COVID-19 pandemic, which have drastically increased the risk of developing mental and/or substance use disorders, overdosing, committing suicide, etc. (33–35).

Figure 1.1 Proportion of total disability-adjusted life years in high-income countries attributable to each main cause group for persons aged 0–24 years in 2010



Legend: Mental and substance use disorders represent the biggest proportion of total disability-adjusted life years in high-income countries for persons aged 0–24 years in 2010. Taken from Erskine et al., 2018 (28).



Figure 1.2 Leading causes of total burden by age group in Australia in 2015

Legend: Suicide and self-inflicted injuries, anxiety disorders, and depressive disorders represent the first, second and third leading causes of burden in young people aged 15–24 respectively. Taken from the Australian Institute of Health and Welfare, 2019 (30).

1.1.3. Opioid overdose crisis

The opioid overdose crisis is threatening the life expectancy of a generation of Canadians and Americans (36). Thousands of lives are being lost every year, in large part due to major shifts in the drug market towards high potent opioids and changing pattern of substance use, in synergy with a neglected low quality treatment system (37).

The health authorities in Canada officially acknowledged opioid overdoses as a crisis in 2016, at the same time that British Columbia declared it a provincial public health emergency (38). Since then, over 17,000 apparent opioid-related deaths have occurred in Canada (39). Despite the medical advancements in other aspects of life, the opioid overdose crisis, and specifically opioid overdoses among young adult men, has offset nearly all the gains in life expectancy from other causes: the life expectancy at birth in Canada did not increase from 2016 to 2017, which had not happened in over 40 years (Figure 1.3) (40,41). In British Columbia, the epicentre of the crisis in Canada, over 20% of all overdose deaths occurred in individuals under the age of 30 (42). The United States declared the opioid epidemic a public health emergency in 2017 (43). The most recorded in the US. Roughly 4,800 of those overdose deaths recorded in 2019 were among individuals between 15 and 24 years of age (44). Adolescents and young adults evidently play a significant role in the ballooning opioid overdose crisis, so much so that overdose deaths among youth are contributing to noticeable changes in life expectancy.

Figure 1.3 Contribution of all-cause age-specific mortality rates to the change in life expectancy at birth from 2016 to 2017, by sex



Legend: Negative changes in life expectancy among adolescent and young adult men and women, offsetting life expectancy gains in older adults. Taken from Statistics Canada, 2019 (41).

The opioid overdose crisis has been evolving continuously since its beginning. At the turn of the century, overdose deaths were largely attributable to prescription opioids, which were then succeeded by dramatic increases in overdose deaths due to heroin (Figure 1.2). These first two waves were then surpassed by alarming levels of overdose deaths due to synthetic opioids, especially fentanyl (Figure 1.2) (45,46). In recent years, the supply of heroin has changed, moving towards rampant and persistent adulteration of heroin with synthetic high potent opioids (47,48). In Canada, 75% of all opioid-related deaths showed fentanyl in 2020, compared with 55% only 3 years prior (39). In the United states, roughly 70% of overdose deaths showed synthetic opioids in 2018 (49). The described changes are especially dangerous for youth who do not have an established opioid tolerance and are starting to explore street drugs. The increased

presence of fentanyl in the drug market has also been reflected in other illicit drug samples, not only heroin (50). Given the popularity of ecstasy, ketamine, LSD, cocaine and methamphetamine (also known as 'club drugs') among youth, especially in the context of raves, nightclubs and festivals, this is a significant concern with possibly fatal consequences (51). For youth growing up in the midst of the opioid overdose crisis, explorative substance use patterns, which are common at this age, have deadly consequences given the presence of highly potent synthetic opioids in the drug supply. In addition, youth have a poor awareness of their own tolerance to substances due to their limited experience with them, and are less aware of, or troubled by, risk factors associated with their substance use. The amalgamation of these predispositions contributes to the heightened vulnerability of youth to engaging in risky drug-taking behaviours or dying prematurely due to accidental injury, suicide, and overdose (21,52–54).



Figure 1.4 Opioid overdose deaths by type of opioid in the United States

Legend: Three waves of opioid mortality: overdoses related to opioid pills, overdose deaths due to heroin, overdose deaths due to fentanyl and other synthetic opioids of illicit supply. Taken from Ciccarone, 2018 (46).

1.1.4. COVID-19 pandemic

The effects of the opioid overdose crisis have devastated communities and families across the world, which are also exacerbated by the COVID-19 pandemic. Addressing the gaps in health care systems of countries around the world are made even more urgent during this pandemic. Substance use and deterioration of mental health symptoms have been reported amongst all demographics, and particularly among university students (55–60). Amidst the chaos and uncertainty, youth represent a particularly vulnerable and at-risk group. Closures to schools and universities, reduced access to health and social services, as well as the diminished social connection and support caused by the self-isolation and quarantine protocols are having catastrophic consequences on the physical, social and mental health of children, adolescents, and young adults (61,62). In a cross-sectional survey study of over 2,000 US college students, almost 50% reported moderate-to-severe levels of depression, close to 40% reported moderate-to-severe levels of anxiety, and one-fifth reported having suicidal thoughts during the pandemic (63). Moreover, in a survey sampling close to 70,000 students living in France during COVID-19 quarantine, the prevalence of suicidal thoughts, severe depression, high level of perceived stress, and high level of anxiety were 11.4%, 16.1%, 24.7%, and 27.5% respectively (64). Of note, the spate of student suicides in and around Las Vegas, Nevada pushed the school district (fifth largest in the United States) to phase in the return of students, despite the high numbers of COVID-19 cases and deaths in the region (65). Also, disrupted mental health services compound the effects of the pandemic as in-person services and peer support groups have been cancelled or have been heavily restricted in capacity, while support by phone or online can be challenging and disengaging for some (66,67).

The challenges brought on by the COVID-19 pandemic have also affected the illegal drug supply, leading to the worsening of an already dire situation (68–70). Business closures, border closures, physical distancing directives and other COVID-19-related social changes have led to decreases in availability, increases in prices, and increases in drug adulteration (71). In British Columbia, since the start of the pandemic, more people have died of drug overdose than of COVID-19 (Figure 1.5); from March 2020 to May 2021, there have been 1,683 deaths from COVID-19 and 2,423 overdose deaths (42). Overdose deaths are continuing to break records across almost all age groups (Figure 1.6).



Figure 1.5 Number of deaths from overdoses and COVID-19 in BC between March 2020 and May 2021.

Legend: Overdose deaths surpassed COVID-19 deaths in BC.



Figure 1.6 Age-Specific Illicit Drug Toxicity Death Rates per 100,000, in BC (2011-2021)

Legend: Increases in illicit drug toxicity deaths rates per 100,000 in British Columbia among all age groups from 2011 to 2021.

1.1.5. Leading cause of death

Of obvious public-health significance is the enhanced risk of premature death that is associated with mental health and substance use disorders among young people. Overdose and suicide are two of the most severe manifestations of mental health distress and high-risk substance use, and are the leading contributors to mortality among youth in North America (31,32).

In 2019 in Canada, over 600 individuals between 15 and 24 years of age died of accidental deaths and unintentional injuries, which includes accidental poisonings (overdose), as well as motor vehicle accidents and falls (31). That same year, close to 500 people aged 15-24 died from suicide in 2019 in Canada. No other causes of death even come close; the third leading cause of death are malignant neoplasms, with 147 deaths in 2019 (Figure 1.7).



Figure 1.7 Leading causes of death by year among individuals between 15 to 24 years old in Canada

Legend: Unintentional injuries and intentional self-harm represent the two leading causes of death among individuals between 15 and 24 years of age in Canada.

A similar situation is observed in the United States. Over 12,000 individuals between 15 and 24 years of age died of accidents or unintentional injury in 2018, and over 6,200 died of suicide (32) (Figure 1.8). Among all unintentional injury deaths, motor vehicle traffic deaths are still the leading cause of death for adolescents and young adults aged 15–24, accounting for roughly 50% of unintentional injury deaths, poisonings accounting for the second most among unintentional injury deaths (35.2%) (32) (Figure 1.9). However, death rates from motor vehicle accidents have generally declined between 2000 and 2018, whereas those for drug overdose deaths have continuously increased (49,72) (Figure 1.10). These trends are due to several factors. For instance, changes in roadway design and vehicle crashworthiness, as well as campaigns to reduce drunk driving and increase seatbelt use have shown decreases in motor vehicle crashes (73). On the other hand, drug overdose deaths are skyrocketing across North America in large part due to an increasingly toxic drug supply in the context of the opioid overdose crisis.



Figure 1.8 Leading causes of death among individuals between 15 to 24 years old in the United States in 2019

Legend: Unintentional injury and suicide as the two leading causes of death among individuals between 15 and 24 years of age in the United States in 2019.



Figure 1.9 Leading causes of unintentional deaths among individuals between 15 and 24 years old in the United States in 2019

Legend: Motor vehicle accidents and poisonings (i.e. overdose deaths) lead all unintentional deaths among individuals between 15 and 24 years of age in the United States in 2019.

Figure 1.10 Number of drug overdose deaths and motor vehicle deaths among individuals between 15 and 24 years old in the United States since 2000



Legend: Increase in drug overdose deaths and decrease in motor vehicle deaths among individuals between 15 and 24 years old, between 2000 and 2019 in the United States.

Deaths from overdose or suicide are the leading contributors to mortality in youth across North America. Though the contamination of street drugs with high potent opioids is a significant and increasing problem, young individuals interacting with such a deadly drug market need appropriate support and services, as well as effective prevention and treatment approaches from functional systems of care.

1.2. Rationale

If it is not met with a consistent system response, the burden due to mental health and substance use disorders will likely continue to escalate among youth in the coming years. Given the alarming overdose and suicide rates within this demographic, there is a pressing need to critically evaluate the current treatment systems in place addressing substance use among youth and to address the gap in the field of youth mental health and addiction. Especially now, at the intersection of two public health emergencies, healthcare systems globally must respond to the mental health and substance use needs of youth. Current systems of care must address the complex and multifaceted needs of youth, who are in critical biopsychosocial developmental periods and experiencing unique neurodevelopment and psychosocial milestones.

This thesis investigates the current treatment paradigm surrounding substance use disorder (SUD) among youth and attempts to shift the paradigm towards more progressive and effective approaches. In doing so, this thesis identifies critical problems in the current system of care as well as raises awareness to the problem of overdose among youth. Insight gained from this thesis will contribute to a more effective response to the opioid crisis among youth and provide a framework for the improved treatment of high-risk substance use among this group.

1.3. Objectives

The main objective of this thesis is to contribute to a shift in the treatment paradigm of mental health and SUDs among youth, addressing the gap within the field of addiction psychiatry and adolescent medicine. This shall be achieved by assessing the current reality of treatment approaches for high-risk substance use among youth, evaluating the existing treatment guidelines

for youth with high-risk substance use, and developing an international consensus on the prevention, treatment, and management of high-risk substance use among youth.

The specific objectives are the following:

1.3.1. Current treatment approaches

The nature of opioid use as well as first-line treatment options have changed dramatically in the past decades. Illicit drugs are trending towards synthetic highly potent opioids, and such shifts are dismantling treatment systems. For adults, treatment approaches for OUD have progressed away from abstinence-based interventions, towards harm reduction measures and pharmacotherapy interventions. The treatment system for youth needs to adapt in accordance with these changes. The objective of this first section is to present the treatment approaches for youth with high-risk opioid use, determine whether the literature supports the use of opioid agonist treatment among youth, and identify evidence for better treatment outcomes in the younger population.

Hypothesis 1: There is little-to-no clinical research on treatment needs and effective interventions among youth with high-risk opioid use.

Hypothesis 2: Medications for OUD are beneficial for youth, and pathways to OAT should be more readily offered in pediatric primary care.

1.3.2. Clinical practice guidelines

Medicine is not only driven by evidence but also by political bias like prohibition and abstinence. Clinical practice guidelines reflect the political, legal, and clinical reality of treatment. They are developed to bridge the gap between research and practice in order to equip healthcare providers with updated treatment resources and recommendations, overturn outdated beliefs, and improve consistency of care. The objective of this second section is to review the international context surrounding clinical practice guidelines on the treatment and management of high-risk opioid use among youth and highlight the manner in which these guidelines have been applied in the clinical field. Hypothesis 1: There is an overall lack of guidance, structural ideas and treatment concepts surrounding high-risk opioid use and opioid use disorder among youth.

Hypothesis 2: The treatment guidelines that exist for high-risk opioid use and opioid use disorder among youth are either outdated or not being implemented appropriately.

1.3.3. International consensus

Good clinical recommendations that promote interventions of proven benefit and discourage ineffective ones have the potential to improve quality of life as well as reduce morbidity and mortality. The lack of youth-focused substance use treatment guidelines represents a missed opportunity to educate treatment systems, prioritize prevention and early intervention, and promote access to appropriate treatment resources. The objective of this third section was to obtain a consensus statement for the prevention, treatment, and management of high-risk substance use in adolescence and early adulthood.

Hypothesis 1: All evidence-based intervention strategies are important to explore with young patients, including pharmacotherapy, and should be used according to the needs and preferences of the patients for maximal engagement.

Hypothesis 2: Mental health and substance use services must address the specific preventative and therapeutic needs of vulnerable youth by being developmentally appropriate, substance-specific, severity-specific, and risk-specific.

Hypothesis 3: Treatment settings and professional teams must receive education and training for proper management of high-risk substance use among youth.

2. Current Treatment Approaches

2.1. Introduction

This first section of the thesis is important in setting the stage, as it provides an overview of the current reality of treatment approaches for high-risk substance use among youth. By developing a comprehensive understanding of up-to-date evidence-based interventions, all subsequent sections of this thesis will be able to build from a firm foundation of knowledge.

2.1.1. High-risk opioid use

High-risk opioid use is a leading cause of morbidity and mortality among youth in the United States (74). Drug-induced death in this population rose from 8.2 per 100,000 in 2010 to 11.2 per 100,000 in 2019 (49). Similarly, in Canada, about a fifth of all illicit drug deaths occurred below 30 years of age (39) In the province of British Columbia alone, drug-related death rates per 100,000 rose from 0.4 to 2.0 for those under 19 years, and from 5.9 to 40.2 for those aged 19-29 between 2010 to 2020 (Figure 2.1) (75).



Figure 2.1 Illicit drug toxicity death rate per 100,000 in British Columbia for youth

Legend: Increase in drug-induced death rates among individuals under 19 years of age (blue) and between 19 and 29 years of age (orange) from 2010 to 2020 in British Columbia.

2.1.2. Benchmarks

Adolescents and young adults are a key population in the opioid overdose crisis. For many of today's young opioid users, initiation of nonmedical prescription opioid use in mid-adolescence provides the entryway into long-term opioid use (76). Prescription opioid misuse, often defined in the literature as the medical misuse of prescription opioids for reasons other than prescribed, or not taken as prescribed (higher doses, snorting, injecting), and/or use without a prescription, is extremely prevalent in youth, with first experiences typically occurring in social settings with the intent on getting high and satisfying curiosity (76,77). Among adolescents, the most common source to obtain prescription opioids for misuse is from friends, relatives or household sources for free (78). Annual prevalence estimates range between 4.8-7.5% among adolescents and 7.6-13.2% among early adults in the US (79).

However, nonmedical use of prescription opioids is a serious concern among adolescents and emerging adults (80). Prescription opioid misuse in youth is significantly associated with all major risk behaviors, including risky driving behaviors, violent behaviors, risky sexual behaviors, other substance use, and suicide attempts (81,82). Moreover, over one-third of adolescents who misused a medication in the past year will go on to develop one or more symptoms of a SUD (83). In a study of over 500 adolescents and young adults who reported past-month nonmedical use of prescription opioids use and/or heroin use, the average age of first prescription opioid misuse was roughly 17 years old, and regular prescription opioid misuse roughly 1-2 years later (Figure 2.2) (76). Transitioning from prescription opioids to heroin use and heroin injection was common and quick, occurring at roughly 19.6 and 20.3 years of age respectively. Although this trajectory is not uniform or inevitable as proportions of youth do not progress to each subsequent benchmark, the common sequence of transitions within similar timeframes does demonstrate a clear pattern of distinct opioid related behaviors in adolescence and young adulthood. Moreover, these trajectories progress at lightning speeds, which leave little room for community-level and structural interventions to prevent, delay or attenuate the escalation of opioid use in young people.



Figure 2.2 Benchmark behaviors in opioid use trajectories

Legend: This figure illustrates the age of onset of benchmark behaviours of opioid use progression in chronological order: first nonmedical prescription opioid use, first regular prescription opioid use, first heroin use, first treatment, first overdose, first regular heroin use and first heroin injection. Data taken from Guarino et al., 2018 (76).

2.1.3. Receipt of treatment

Unfortunately, only a small portion of youth with high-risk opioid use receive any effective treatment. In a study by Alinsky et al. (2020), of over 3600 youths between 13 and 22 years of age who experienced a nonfatal opioid overdose, close to 70% received no addiction treatment within 30 days after the overdose (84). Less than 30% received behavioral health services alone, and roughly 2% received pharmacotherapy (84). This is dramatically less than what is offered to adults: roughly 45% adult received behavioral health services and 17% receive pharmacotherapy within 30 days of opioid overdose (85,86). The treatment for youth has been predominantly focused on abstinence-based psychosocial interventions as well as short-term inpatient detoxification (87–89). Even within treatment programs, youth are provided with less pharmacotherapeutic options than adults, which emphasizes the large unmet need for addiction treatment in younger populations (84). For instance, 26% of adult in treatment for heroin addiction receive pharmacological treatments, relative to about 2.5% of adolescents (90). The

full range of treatment options, especially OAT and relapse prevention, are highly inaccessible for youth (91). The existing treatment approaches for youth do not compare to the main treatment options for adults in terms of quality of care.

2.1.4. Treatment in adults

In adults, there are various treatment strategies available for opioid dependence, including abstinence-based programs starting with detoxification and followed by psychosocial rehabilitation, counselling programs, as well as opioid agonist treatment (OAT), the most effective intervention. Standalone detoxification has been found to be ineffective in adults, as it may leave patients vulnerable to overdose upon relapse as a result of the rapid loss of tolerance to opioids, as well as more likely to contract HIV and Hepatitis C infections as a result of high-risk behaviors upon relapse (92–95). The gold standard of treatments for adults is OAT and has been shown to be superior to detoxification for the majority of users in terms of retention in treatment, sustained abstinence from opioid use, and reduced risk of morbidity and mortality (96). OAT for the treatment of opioid dependence has been endorsed by most medical societies (74,97–99).

2.1.5. Treatment in youth

The limited clinical practice guidelines that exist recommend clinicians to consider treating youth who have OUD using the full range of treatment options, including pharmacotherapy with opioid agonists (methadone and buprenorphine) and antagonists (naltrexone) (74,99). However, these guidelines acknowledge the confusion, stigma, and limited resources which severely restrict access to medication-assisted treatment for youth, and state that efficacy studies for these medications have primarily been conducted in adults but not in younger populations (74,98). Abstinence-based treatment, or no treatment, still seems to be the most common option in North America, imposed by a lack of specific expertise and resources in this domain. Nearly 90% of youth with SUD in the United States do not receive any treatment, and only 27% of youth diagnosed with OUD were dispensed a treatment medication within 6 months of an OUD diagnosis (100,101). A similar trend is observed in other countries such as the United Kingdom, in which 94% of young people who started a treatment intervention received psychosocial

interventions, 61% received harm reduction services, and less than 1% received a pharmacological treatment (102).

2.1.6. Objective

The nature of opioid use as well as first-line treatment options have changed dramatically in the past decades; the treatment system for youth needs to adapt in accordance with these changes. The objective of this narrative review was to review the treatment approaches for youth with high-risk opioid use, determine whether the literature supports the use of OAT among youth, and identify evidence for better treatment outcomes in younger population. This narrative review is a first step in addressing the broader aim of this thesis by creating a firm foundation of knowledge regarding evidence-based treatment approaches using the current literature on high-risk opioid use in youth.

2.2. Methods

Published scientific literature was obtained from PubMed® using the following medical subheading (MeSH) term combinations: "youth" or "adolescent" or "high school" or "young" and "abuse" or "overdose" or "depend" or "addict" or "intoxication" and "intervention" or "treat" or "outpatient" or "inpatient" or "emergency" or "clinic" or "care", "approach" or "mode" or "therapy" or "psychosocial" or "behavioral" or "detoxification" or "strategies" or "substitution" or "cognitive" or "withdrawal" and "opioid" or "heroin". This literature search was done in October of 2019 and provided us with 1,436 references.

We screened the titles of all references and excluded any that failed to relate to youth and failed to mention a treatment approach (abstinence-based or medication-assisted treatment). This resulted in 137 articles, including six review papers. For the full text screening, we included all studies that reported on outcomes of youth in treatment for opioid use and excluded any study that solely reported on psychosocial interventions. In total, this review includes a total of six review papers, four randomized controlled trials (RCTs), and nine observational clinical studies (Figure 2.3). Documents within the grey literature (government/committee reports, conference proceedings, discussion papers, presentations, etc.) and studies that solely examined

psychosocial interventions were not included in the review but were used to provide context in the introduction and discussion sections of this review.



Figure 2.3 Flow chart of search and review process

Legend: This figure illustrates the methods of this narrative review, which identified 1,436 references in the literature, excluded 1,299 based on title and abstract and excluded 118 based on full-article, resulting in 19 studies included in this narrative review

2.3. Results

2.3.1. Randomized clinical trials

All four identified RCTs evaluated buprenorphine and had opioid abstinence and treatment retention among their primary and secondary outcomes (Table 2.1). All provided psychosocial interventions, but only one reported on patient attendance to sessions. Only two of the four RCTs included participants with concurrent disorders and reported on the prevalence of psychiatric symptoms and disorders within their sample (103,104).

The oldest RCT was an outpatient double-blind, double-dummy 28-day detoxification trial, with participants (N=36) randomized to either buprenorphine or clonidine (105). In addition to the medication, both groups received behavioural counselling and opioid abstinence incentives.
Treatment retention of adolescents was higher and opioid-positive urine tests lower in the buprenorphine than in the clonidine group. Those receiving buprenorphine reported more positive effects of medication while both groups reported relief of withdrawal symptoms and related HIV risk behaviour.

The second trial was a multi-site comparison of patients aged 15-21 with OUD (N=152) randomized to a 14-day or 12-week detoxification in combination with 12 weeks of psychosocial treatment that included weekly individual and group counselling (106). Both groups received buprenorphine/naloxone but patients in the 14-day group ended taper by day 14, whereas patients in the 12-week group ended at week 12. Participants in the 12-week group had lower proportions of opioid-positive urine tests at weeks 4 and 8 but not at week 12. Participants in the 12-week group also reported less opioid use, less injecting, and less non-study addiction treatment. Those who had attended at least two individual or group counselling sessions in the first two weeks were less likely to drop out compared to those with one or no visits, and had lower rates of opioid-positive urinalysis (106,107). Many patients in this trial had concurrent psychiatric symptoms (54.6%), which was not associated with attrition in either group but was associated with lower opioid use (106–108).

The third RCT randomized opioid-dependent young adults receiving 13-week buprenorphine/naloxone treatment (N=80) to memantine or placebo (109). Treatment retention was not significantly different between groups, but memantine 30 mg significantly improved treatment with buprenorphine/naloxone by reducing relapse and opioid use after buprenorphine/naloxone discontinuation. In a secondary outcome study, prescription opioid users had higher retention and compliance rates relative to heroin users, but these differences were not statistically significant (110).

In the last RCT, participants (N=53) were randomized to either a 28-day or a 56-day buprenorphine taper (111). Participants in the 56-day group had significantly higher rates of opioid abstinence and treatment retention. Independent of taper duration, daily attendance requirement was associated with decreased abstinence and shorter retention compared with a biweekly or triweekly attendance requirement.

Authors year	Marsch et al. 2005	Woody et al. 2008	Gonzalez et al. 2015	Marsch et al. 2016
Design	Double blind	Multicenter perellel	Double blind perallel	Double blind placebo
Design	double dummy	groups PCT	groups PCT	pouble-blind, placebo
	norallel groups PCT	groups RC I	groups KC1	PCT
Satting	Liniversity based	6 community programs	Community based	Two hospital hasad
Setting	rasaarah alinia from	from 07/2002 12/2006	community-based	research alinias from
	10/2001 12/2002	110111 07/2003-12/2000.	substance abuse treatment	
Intervention	(1) 28 day outpatient	(1) Maintananaa group:	(1) 12 week hun/nl with	(1) 28 day hup tapar
mervention	(1) 28-day outpatient	(1) Maintenance group.	(1) 13-week bup/iii with	(1) 20-day bup. taper
	(2) 28 day symptom	(2) Detay, groups 14 day	(2) 12 weak hum/ml with	(2) 50-day bup. taper
	(2) 28-day outpatient	(2) Delox. gloup. 14-day		
Davahagaaial	All participants wars		All participants received	Doth groups received
Psychosocial	All participants were	All participants were	All participants received	Both groups received
Intervention	provided with	offered weekly individual	cognitive-benavioral	benavioral counseling
	benavioral counseling	and group counseling.	treatment.	and opioid abstinence
	and incentives			incentives
	abatingent on opioid			
Samula	26 participants hotwar	154 porticipants hatwaan	80 manti aimanta hatwaan	52 participants hatwaan
Sample	36 participants between	154 participants between	80 participants between	55 participants between
	the ages of 15 and 18	met DSM IV aritaria for	the ages of 18 to 25	the ages of 16 and 24
	who met DSM-IV	met DSM-IV criteria for	seeking treatment for	who met DSM-IV
	criteria for opioid	opioid dependence	opioid-dependence	opioid dependence
Davahiatria	ADUD: 419/	A my active	ND	N D
Psychiatric	ADHD: 41%	Any active	N.K.	IN.K.
comorbidity	MDD: 100%	symptom: 54 69/3		
	MDD: 100%	symptom: 54.076		
Outcome	1. Treatment retention	1 Onicid nositivo unino	1 Onioid abstinance	1 Onioid abatinanaa
Outcome	2. Onicid abstinonce	2 Drop out salf reported	2. Treatment retention	2. Treatment retention
	2. Opioid abstillence, HIV risk behavior	2. Diop-out, self-reported	2. Treatment retention,	2. Treatment retention
	withdrawal adverse	additional addiction	depression symptoms	
	events	treatment other drug use	depression symptoms	
	events	adverse events		
Results	Significantly greater	Week 4 61% detoy	Treatment retention was	Participants who
Results	percentage of	natients had positive	not significantly different	received a 56-day hun
	adolescents who	results vs 26%	hetween groups	taper had a significantly
	received hun were	maintenance natients	Among participants	higher percentage of
	retained in treatment	Week 8 54% detox	abstinent on week 8 those	opioid-negative urine
	(72%) relative to those	natients had positive	in the memantine 30mg	tests (35% vs 17%) and
	who received clonidine	results vs 23%	group were significantly	were retained in
	(39%).	maintenance patients	less likely to relapse after	treatment significantly
	Significantly higher	Week 12, 51% detox	bup, was discontinued	longer (37.5 vs 26.4
	percentage of	patients had positive	(81.9%) compared to the	days) compared with
	scheduled urine test	results vs 43%	placebo group (30%).	participants who
	results were opioid	maintenance patients.	1 BP (007.0).	received a 28-day bun
	negative for those in	Week 12, 20.5% detox.		taper.
	the bup. group (64%	patients remained in		1
	compared to 32%).	treatment vs 70.3%		
	¥ - /	maintenance patients.		

Table 2.1. Randomized clinical trials on the treatment of high-risk opioid use in youth

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; bup., buprenorphine; CD, conduct disorder; detox., detoxification; HIV, human immunodeficiency virus; MDD, major depressive disorder; N.R., not reported; ODD, oppositional defiant disorder; RCT, randomized controlled trial; bup/nl, buprenorphine/naloxone. ^a Reported in secondary analysis in Warden et al., 2012.

2.3.2. Observational Studies

Nine observational studies were identified, including one prospective cohort studies, three retrospective chart reviews and five retrospective cohort studies that evaluated treatment approaches in inpatient and outpatient settings among youth with high-risk opioid use (Table 2.2). Among the nine included in this review, four examined buprenorphine only, two examined methadone only, one examined buprenorphine and extended-release naltrexone, and two examined buprenorphine and methadone. Additionally, within the nine observational studies, only one study described how pre-existing mental health conditions affected treatment outcome (112). Of the remaining studies, five did not report on psychiatric comorbidities, while the remaining three simply reported prevalence, which was between 50% and 90% (113–115).

Three retrospective cohort studies reported 1-year retention rates for buprenorphine treatment near 10% (112,116,117). Retention rates were much higher at the beginning of buprenorphine treatment: 69.9% at 30 days reported by Mutlu et al. (N=112), 45% at 60 days reported by Matson et al. (N=103), and 33.8% at 90 days reported by Dayal and Balhara (N=68). A crucial point in time in Mutlu et al. (2016) seemed to be at 60 days, as about half of patients discontinued buprenorphine treatment and relapsed within the first two months - the reasons for discontinuation and relapse were not documented (112). Additionally, patients admitted for 2-8 weeks of inpatient treatment had significantly better retention and abstinence rates, as well as more intensive counselling relative to outpatients (112,116,117).

In a prospective cohort study (N=75), 53% of participants completed a 9-month outpatient buprenorphine treatment, with significant and persistent reductions in drug use (118). The majority (88%) remained in counselling for the duration and attendance to sessions was 74%. After nine months of OAT, patients underwent detoxification, at which point psychiatric problems increased beyond pre-treatment levels. During this tapering phase, three patients died (heroin/benzodiazepine overdose, suicide and traffic accident, respectively) (118).

In the retrospective chart review (N=56), patients received buprenorphine or extended-release naltrexone based on patient preference and clinical recommendations (113). There were no significant differences in retention and opioid-negative urine tests between the two groups.

Retention rates for the entire sample were 65% at 12 weeks and 40% at 24 weeks, whereas opioid-negative rates were 50% at 12 weeks and 39% at 24 weeks (113).

Literature on methadone treatment for youth was sparse - two studies that reported retention and abstinence were identified. One study (N=37) found a higher retention rate among individuals receiving methadone for more than 60 days, relative to those receiving methadone for 60 days or less (119). Another cohort study (N=147) evaluating the impact of methadone treatment on opioid-dependent youth found a retention rate of 48% at 12 months (114). Among patients who stayed in treatment for more than one year, there was a significant reduction in heroin use (114).

Two retrospective cohort studies reporting on methadone and buprenorphine treatment among youth were identified. For both studies, OAT with methadone had higher completion and retention rates, whereas buprenorphine had higher drop-out and transfer rates (115,120). One of the studies (N=100) found that 21% of patients who initiated treatment with buprenorphine switched to methadone within the first three months (115). In the second study (N=61), methadone treatment had significantly longer initial retention and slower treatment re-entry, as compared to the short and frequent episodes observed in buprenorphine treatment (120,121).

Authors, year	DeAngelis et al., 1973	Kellogg et al., 2006	Bell & Mutch, 2006	Kornør et al., 2006	Smyth et al., 2012	Matson et al., 2014	Mutlu et al., 2016	Vo et al., 2016	Dayal & Balhara, 2017
Type of	Cohort	Cohort	Retrospecti	Cohort	Retrospecti	Retrospecti	Retrospecti	Retrospecti	Retrospecti
study	study	study	e chart review	study	ve cohort study	ve chart review	ve cohort study	e chart review	e cohort study
Mean age	19	19.6-18.8	16.2	26.2	16.6	19.2	16.9	23.1	22.4
Sample size	37	147	61	75	100	103	112	56	68
Medicati	Methadon	Methadon	Methadone,	Bup.	Methadone	Bup/nl	Bup/nl	Bup., ER-	Bup.
on	e	e	bup.		bup.			nalt.	
In-	Outpatien	Inpatient	Outpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient
patient or	t	and			and		and		and
out-		outpatient			outpatient		outpatient		outpatient
patient		-			-		-		-
Intervent	Methadon	Methadon	Methadone	9-month	Methadone	bup/nl	8-week	Specialty	bup/nl
ion	e	e	maintenanc	bup.	maintenanc	treatment	bup/nl	community	treatment
	treatment	maintenan	and bup.	replaceme	e (81%) and	program	treatment	treatment	program
	program	ce	maintenanc	nt program	bup.		program	program	
	followed	treatment		_	maintenanc				
	by detox				e (19%).				

Table 2.2 Observational studies on the treatment of high-risk opioid use in youth

Treatmen t retention	Average of 85 days in methadon e treatment; 35% in the study until completio n	48% at 1 year	23.5% for methadone 12% for bup.	53% at 9 months	At 3, 6, and 12 months after treatment start, 63%, 55%, and 50% of patients were retained.	45% at 60 days 9% at 1 year	69.6% at 30 days 16.1% at 1 year	65% at 12 weeks 40% at 24 weeks No significant differences between groups	33.8% at 90 days 19.1% at 6 months 11.7% at 1 year
Opioid abstinenc e	Average of 77 days drug-free after detoxificat ion	N.R.	N.R.	N.R.	Among those in treatment at 12 months, 39% demonstrate d abstinence.	85.2% overall	69.0% at 30 days 10.3% at 1 year	50% at 12 weeks; 39% at 24 weeks No significant differences between groups	N.R.
Psychosoci al Interventio n	Group therapy, individual counselli ng, mock speaking, education programs, recreation al activities, tutoring, arts therapy.	Weekly appointme nts with counselor and available group sessions.	N.R.	Multi- disciplinar y, eclectic therapeutic approaches , individual sessions of diverse intensity, behavioura l therapy group sessions	CBT, motivationa l interviewin g, individual therapy, family therapy, group activities, art therapy, delivery of life skills	Drug rehabilitation n program or a patchwork program of individual counseling and 12-step meetings	Weekly individual and group drug counselling and behavioral therapy available.	Group and individual counsellin g, physician visits for manageme nt of medication , and mental health therapy and psychiatric treatment	Counselling and rehabilitation n services
Program retention	N.R.	N.R.	N.R.	88% of participant s remained in psychosoci al interventio ns for the entire bup. program	N.R.	N.R.	Day 30: 81% Day 60: 64% Day 180: 39% 1 year: 24%	No differences between groups in program attendance	N.R.

Abbreviations: bup., buprenorphine; bup/nl, buprenorphine/naloxone; CBT, cognitive behavioural therapy; ER, extended release; Nalt., naltrexone; N.R., not reported.

2.3.3. Reviews

Six reviews (two systematic and four narrative) on treatment of opioid-dependent youth were identified (Table 2.3). A systematic review from the Cochrane Database identified only two RCTs and therefore found it difficult to draw a conclusion due to lack of evidence (122). Another review suggested reconsideration of the traditional opposition to OAT among youth but

highlighted the need for more studies (123). A third review suggested that length of time in treatment was the best predictor of outcome, regardless of modality, but added that research on treatment initiation and retention of specifically designed programs for youth was lacking (124). A fourth review emphasized the need for better detection of OUD to increase the number of youths who receive referrals to addiction experts and suggested the widespread use of validated screening tools and improved access to OAT (125).

Only one review focused on pharmacological interventions such as methadone, buprenorphine, and naltrexone for youth with OUD (126). It concluded that the implementation of medication-assisted treatment as standard practice is feasible in specialty care settings, easily integrated with counselling or psychotherapy, and has the potential to greatly improve treatment outcomes (126). In agreement with this review, the sixth review recommended that youth as young as 16 years of age with OUD should go through at least 12 weeks of buprenorphine treatment, with no obligation of discontinuing (127). Though methadone treatment is mentioned by some of the reviews, most describe the widespread unavailability of methadone and its inaccessibility due to regulatory barriers (126,127).

Authors, year	Hopfer, et al., 2002	Subramaniam et al., 2009	Pecoraro et al., 2013	Minozzi et al., 2014	Borodovsky et al., 2019	Eisdorfer & Galinkin, 2019
Туре	Systematic	Narrative	Narrative	Systematic	Narrative	Narrative
Sources	Medline, PsycINFO	Reference lists of articles	Reference lists of articles	Cochrane Library, PubMed, EMBASE, CINAHL, Web of Science, reference lists of articles.	PubMed, PsycINFO, Web of Science, Cochrane Library, NIDA Clinical Trials Network Dissemination Library, NIDA Data Share, SAMHSA websites.	Reference lists of articles
Articles	15	2	6	2	12	4

Table 2.3 Reviews on the treatment of high-risk opioid use in youth

Conclusions	Option of methadone should be seriously considered. Sparse research literature has not addressed the question of whether treatment specifically designed for youth would be more effective at attracting and	More research is needed for several clinically relevant areas: appropriate duration of OAT, ways to enhance adherence, the value of integrated treatments for co-occurring conditions, and the role of opioid antaganists in	Concerns about safety and efficacy with youth require more research Opioid-dependent youth should be considered candidates for OAT delivered in a comprehensive, developmentally appropriate context.	Review was limited by the very low number of trials and the very low quality of evidence retrieved.	No single approach to treatment for all youth. Treatment plans need to be tailored to individual needs. OUD in youth is a chronic medical condition, requiring long- term management strategies that include bup. as	Children and adolescents are at risk for opioid misuse, and early detection is imperative to facilitate treatment and improve outcomes.
	effective at attracting and retaining youth.	opioid antagonists in treatment			include bup. as one of the first- line treatments.	

Abbreviations: bup., buprenorphine; NIDA, National Institute on Drug Abuse; OAT, opioid agonist treatment; OUD, opioid use disorder; SAMHSA, Substance Abuse and Mental Health Services Administration.

2.4. Discussion

Opioid-related overdose deaths in youth have been increasing in recent years (49). There is a dearth of needs-adapted treatment options contributing to the majority of youth not being in substance dependence care, even after an overdose. There is also little clinical research on treatment needs and effective interventions among youth that use opioids. Though OAT is globally preferred for adults, little research has been done to evaluate the effect of this treatment option in youth (96). The strongest conclusions made by this review are that medications for OUD seem to be beneficial for youth and that pathways to OAT should be more readily offered in pediatric primary care. Research should prioritize youth-specific interventions in order to decisively determine the safety and efficacy of OAT in youth.

Policies that restrict youth from accessing pharmacotherapy despite the evidence add roadblocks to research (128). The scarcity of the literature and the difficulty in finding relevant articles has been reflected in this review and highlighted in others (124). Although preliminary evidence suggests that the use of methadone and buprenorphine are effective and safe, there are few studies examining the efficacy of these programs among youth (129,130). Though these conclusions have been reported in similar reviews, it is important to update and extend the findings given the current opioid overdose crisis in several countries.

2.4.1. Treatment Options

Studies included in this review primarily looked at buprenorphine, methadone and naltrexone, which are also among the most common medications used in OAT for adults. The literature identified in this review has primarily examined the feasibility and efficacy of buprenorphine/naloxone among youth. Buprenorphine/naloxone is currently approved for OUD at age 16 in the United States and at age 18 in Canada (131). Methadone can be prescribed to youth under the age of 18 but the United States Code of Federal Regulations requires documentation that the patient has failed two previous drug-free or withdrawal management attempts and has written consent from a parent or guardian (129,132). As well, most methadone programs are prohibited from admitting patients younger than 18 years, which may explain why there is a lower number of youth receiving methadone relative to buprenorphine (74,133). The third common medication used, oral naltrexone, has been FDA-approved for adults (≥18 years) since 1984, and the FDA approved the long-acting injectable formulation in 2010 (100).

2.4.1.1. Buprenorphine

The literature has primarily examined the feasibility and efficacy of buprenorphine/naloxone among youth. OAT with buprenorphine has been found to be effective in youth with OUD (103,134). Concerning detoxification, longer taper periods seem to be most desirable (111). Retention rates and opioid abstinence rates for buprenorphine maintenance have been reported to be around 50% and 30% respectively at 12 months, which appears to be lower relative to adults (113,135–139). This may be due to the lack of buprenorphine treatments specifically catered to youth, addressing their unique developmental challenges. Buprenorphine's potential risk for misuse and diversion, as well as it's complicated and long induction, likely have a role to play in its lower retention rate (140). Innovative induction protocols have been developed clinically to improve the accessibility and acceptability of buprenorphine for young patients (141,142).

2.4.1.2. Methadone

Evidence suggests that methadone may be more effective than buprenorphine in terms of treatment retention and opioid abstinence among youth, which is consistent with prior research among adult samples (143). Reasons for the better retention associated with methadone relative

to buprenorphine may be due to differences in policy or programmatic issues, which may contribute to the varying access of each medication, as well as to the clinical approach of each medication, including dose range and dosing strategy. Higher dosages of methadone and individualization of doses have been independently associated with better retention in methadone maintenance treatment (144). Nevertheless, each substance has unique benefits and challenges that are impacted by individual preferences, context of use, accessibility and cost (145,146). In countries such as the United States, United Kingdom, and Australia, methadone is the most common medication, but buprenorphine is increasingly promoted by providers (147–149). In others, like Canada and France, methadone is recognized as second-line treatment in adults after buprenorphine, despite much higher costs of the latter (150–152).

2.4.1.3. Naltrexone

The least studied medication was extended-release naltrexone, which had promising results since the retention rate of individuals taking naltrexone was not significantly different from those taking buprenorphine (153). Though oral naltrexone has been associated with relapse and fatal overdose, extended-release naltrexone may be a promising and feasible third-line treatment (129). More studies of extended-release naltrexone in youth are required before confidently adding it to the range of medications for OAT (154).

2.4.1.4. Other Medication Used in Conjunction

Several medications have been used alongside buprenorphine and methadone, but with varying effectiveness. Antidepressants in methadone programs were not significantly associated with a reduction in relapse risk (155). Though memantine did not significantly improve retention, it did significantly improve short-term treatment with buprenorphine/naloxone for opioid-dependent young adults by reducing relapse and opioid use (156). However, these findings are to be considered within the very limited clinical work regarding the use of memantine in OUD. For instance, memantine did not increase treatment effectiveness in a double-blind study with opioid-dependent participants receiving extended-release naltrexone (157). Further research should explore how combining short-term symptomatic medication with buprenorphine/naloxone or methadone may be an effective alternative treatment to long-term methadone or buprenorphine maintenance in young adults.

Other effective pharmacotherapies used in adult treatments have not been studied in youth. These include slow-release morphine, hydromorphone, diacetylmorphine and levomethadone, which are evidence-based treatments approved in some countries (158–162). Since each medication has unique benefits and challenges that are impacted by individual preferences, settings of use, accessibility and cost, increasing the available treatment options offered to youth overall will ultimately lead to better adherence and treatment outcomes (145). In order to gain more information about the effectiveness, safety and tolerability of OAT and other medication-assisted treatment approaches in patients aged 18 to 25 years, data on this patient subpopulation can be extracted from completed clinical trials and observational studies among adult populations.

2.4.2. Concurrent disorders and psychosocial treatment

In the studies identified, the majority either excluded patients with psychiatric illnesses or simply reported the prevalence of psychiatric comorbidities within the sample. Only a handful of studies assessed the psychiatric disorders in relation to the treatment outcomes. Most of the studies identified in the review did not isolate the impact of psychosocial interventions from the therapeutic effect of the pharmacological treatment, since it is impossible to quantify the 'dose' of the psychosocial component (127,163). For most buprenorphine and methadone programs included in the review, individual counselling, group sessions, and family therapy were offered but not mandatory (113,164). As a result, they were often not factored in the analysis, and were solely used to enhance treatment (113,115,139,156,164,165).

The low retention of youth in care can be partly explained by the failure to address their specific needs and recognize critical developmental vulnerabilities (138,166,167). Adolescence and young adulthood are characterized by unique neurodevelopmental and psychosocial milestones, with greater vulnerability for substance misuse due to on-going prefrontal cortex development, the area of the brain most involved in attention regulation, inhibition of impulses and anticipation of the consequences of actions (133,168,169). Additionally, factors such as early childhood trauma, complex familial situations, and co-occurring disorders are prevalent in young individuals with SUDs (170,171). Of the articles that reported on psychiatric comorbidities, the prevalence was high, between 50% and 90%, highlighting the importance of addressing

concurrent disorders (103,113,115,164). Appropriately integrating psychosocial interventions into the continuum of care for youth can be an effective way of addressing comorbid psychiatric conditions and emotional drivers of substance use, leading to improved retention and treatment trajectories (163,172–174).

2.4.3. International Perspective

Some European countries seem to favour integrative and patient-centered approaches much more. In Germany for instance, treatment agreements between the client and their provider clearly stating the steps and objectives within the framework of treatment contracts are common and have been found to improve adherence and outcomes of OAT (175). Similarly, regulations of OAT in Germany have made psychosocial interventions mandatory adjunct to any OAT (149). Comprehensive approaches to treatment have proven to be effective for adolescents in substance abuse treatment in Europe (176). However, the existence of specific youth-oriented guidelines on a European level is scarce and lacks a strong evidence base. There is a need to identify and expand treatment effectiveness in order to share common models of good practice.

2.4.4. Limitations

This review is not without limitations. The search strategy was specific to peer-reviewed publications, therefore documents and reports from governing bodies and medical associations could not be included extensively. Also, this review only included publications written in English, potentially excluding relevant studies from non-English speaking research groups. Finally, this may not be an exhaustive search, as after completion, an additional review was published by Camenga et al. synthesizing the evidence on the efficacy and potential risks associated with methadone, buprenorphine or naltrexone for the treatment of OUD in adolescents (177). Their findings are in support of the conclusions drawn by this review, in that the risks of untreated OUD far outweighed the risks of using any of the OAT medications, and that more research is indeed needed (177).

2.5. Conclusion

The objective of this narrative review was to present the treatment approaches for youth with high-risk use, determine whether the literature supports the use of OAT among youth, and

identify evidence for better treatment outcomes to the younger population. Overall, the principal finding of this review is that OAT should be a key factor in the treatment trajectory of youth with OUD. Treatments offered to youth with high-risk opioid use were found to be less effective to those for adults, possibly due to the lack of youth-specific interventions and the incompatibility of youth in adult treatment programs. Treatment goals of prescribing clinicians in the few studies available were based on different provider preferences and the range of therapeutic options offered to youth was much too small. Limited access and legislation for prescribing the full spectrum of OAT options are further barriers to youth receiving the care they need. Psychosocial treatments were often offered in the studies included, but this strategy alone is not sufficient to retain patients in care and achieve stabilization.

The lack of academic efforts in this domain are devastating, especially given the low age of first consumption and the enormous burden of concurrent trauma and mental illness among young users. Youth with OUD have not benefitted from the progress that was made in clinical practice for adult opioid users throughout most parts of the world. Despite the growing needs in this age group, there is little research on the clinical treatment of high-risk opioid use and the lack of quality care and treatment coverage is even worse than the situation observed within adult treatment systems. Possible reasons for such a dysfunctional system include a myriad of political and ideological biases centered around abstinence and substance use among youth, which continue to place adolescents and young adults at great risk (178). Based on conclusions from this section, we hypothesize that there is also an overall lack of clinical guidance for high-risk opioid use, and that available clinical practice guidelines are outdated or obsolete. This leaves healthcare providers unprepared to handle high-risk substance use and concurrent disorders among youth, as well as leaves healthcare systems without any capacity to appropriately meet the unique needs of youth.

In the next section, the state of treatment recommendations and practice guidelines internationally will be evaluated. After having reviewed the current literature for evidence-based approaches of high-risk opioid use in youth, the natural next step is to assess the gap between research and practice recommendations by evaluating clinical practice guidelines, or lack thereof.

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3. Clinical Practice Guidelines

3.1. Introduction

The previous section reviewed the current literature on evidence-based treatment approaches for youth with high-risk opioid use. However, medicine is not only driven by evidence but is also influenced by underlying political biases and values. This second section of the thesis will evaluate clinical practice guidelines, or lack thereof, in an effort to assess the political, legal, and clinical reality of treatment, as well as the gap between research and practice recommendations for high-risk opioid use among youth.

3.1.1. Background

Currently, there is a lack of evidence-based interventions in the treatment of high-risk opioid use among youth (122–124). Some clinical research, mainly in the form of observational studies and a handful of randomized controlled trials, has been done on the safety and effectiveness of pharmacological intervention in adolescents. Opioid agonist treatments (OAT) have been shown to work in younger populations. However, the studies have had generally small sample sizes and been low-quality, rendering their clinical utility quite minimal. Nevertheless, the existing literature and most specialists in child and adolescent psychiatry argue that the risks of untreated OUD far outweigh the risks of using any of the OAT medications, despite the urgent need for more research in this field (177,179).

3.1.2. Conservative treatment ideologies

Abstinence-based treatment, or no treatment, appears to be the most common strategy in most parts of the world. Clinicians are more inclined to default to conservative treatment ideologies, such as abstinence-based interventions, instead of prescribing medications due to their unfamiliarity towards treatments such as OAT for youth (100). The low rates and very narrow range of pharmacotherapy for youth compared to adults are driven in part by a great quantity of providers who are unaware and unfamiliar with OAT, as well as a shortage of providers who are willing to prescribe medications for OUD among youth (100,167). The lack of resources for pharmacological treatment programs and lack of physician training have created a large training gap, as only 1% of all US addiction medicine board diplomats are pediatricians (180). Similarly, though pediatricians have access to an AAP-endorsed buprenorphine waiver course, the

requirement for specialized training and certification creates a barrier for providers who may feel like it is too hard or too dangerous (167). Additionally, the limited documented efficacy of these medications in this population have made treatment providers believe that more conservative treatment such as abstinence-based should be tried first (100,181). Many providers view OAT as a 'last resort' for youth due to stigma and misperception of replacing one addiction with another, often waiting until young adults have relapsed or experienced severe adverse consequences (178,181). Treatment providers as well as authoritative members such as family and trusted adults often decide on a treatment trajectory without consulting with the patient (181). Such treatment trajectories are often not nested in established pathways or stepped care model, which can provide evidence-based recommendations for specific diagnoses and specific steps in health care delivery (182).

3.1.3. Objective

Good clinical practice guidelines provide explicit and authoritative recommendations for clinicians, overturn outdated practices, and improve the consistency of care (183). The objective of this study is to critically review guidelines on the treatment and management of high-risk opioid use among youth and to highlight the manner in which these guidelines have been applied in the clinical field. With respect to the thesis, this section will summarize current international guidance in order to more broadly assess the treatment concepts for high-risk substance use within the healthcare system.

3.2. Methods

This study was a rapid review of clinical guidelines for the treatment and management opioid use disorder among youth. Clinical guidelines were defined as systematically developed recommendations produced to direct the management of young patients with high-risk opioid use (184). To be included, guidelines had to make specific recommendations aimed at the care of adolescents and young adults and be written in English. We excluded guidelines that exclusively concerned prevention of OUD or diagnostic studies.

This review included searches of the peer-reviewed literature and the grey literature. Ovid MEDLINE was searched in September 2020 to identify relevant peer-reviewed articles,

performed in consultation with a medical librarian. Ovid MEDLINE covers the international literature on biomedicine, including the allied health fields and the biological and physical sciences, humanities, and information science as they relate to medicine and health care. The CADTH citation search hedge for clinical practice guideline was used, in combination with subject headings and keywords for the opioid dependence and adolescents' concepts (185). The search strategy was then translated to Ovid EMBASE, mapping each mesh term to its equivalent entry term and accounting for all syntactical differences. The search strategy for Ovid MEDLINE is provided in Table 3.1. Searches were limited to papers published from 2010 onwards to ensure that data reflected recent clinical practice. To facilitate a more rapid review, every title and abstract was screened by one reviewer independently. After each reference passed the first screening stage, two reviewers screened the full texts independently. Where conflict about inclusion existed, a third reviewer made the final decision. This is a common search strategy for rapid reviews (186).

Table 3.1 Search strategy for Ovid MEDLINE and Epub Ahead of Print, In-Process & OtherNon-Indexed Citations, Daily and Versions 1946 to Present

	Searches	Results
1	Critical Pathways/	6814
2	exp Clinical Protocols/	168623
3	consensus/	13202
4	exp consensus development conference/	12017
5	exp consensus development conferences as topic/	2860
6	critical pathways/	6814
7	exp guideline/	34365
8	guidelines as topic/	39945
9	exp practice guideline/	27396
10	practice guidelines as topic/	118696
11	health planning guidelines/	4098
12	(position statement* or policy statement* or practice parameter* or best	33739
	practice*).ti,ab,kf,kw.	
13	(standards or guideline or guidelines).ti,kf,kw.	111083
14	(guideline or practice guideline or consensus development conference or consensus	43774
	development conference, NIH).pt.	
15	(position statement* or policy statement* or practice parameter* or best	33739
	practice*).ti,ab,kf,kw.	
16	(standards or guideline or guidelines).ti,kf,kw.	111083
17	((practice or treatment* or clinical) adj guideline*).ab.	40520
18	(CPG or CPGs).ti.	5763
19	consensus*.ti,kf,kw.	26636
20	consensus*.ab. /freq=2	25624

21	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or	20493
	protocol*)).ti,ab,kf,kw.	
22	recommendat*.ti,kf,kw.	41899
23	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or	59816
	plans)).ti,ab,kf,kw.	
24	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or	7747
	diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.	
25	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or	9987
	treatment* or intervention*)).ti,ab,kf,kw.	
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or	621037
	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	
27	exp Analgesics, Opioid/	116335
28	(opium or opiate* or opioid or heroin or medication assisted or substitution treatment or	125237
	maintenance treatment or methadone or levomethadone or buprenorphine or suboxone	
	or (morphine and slow) or diamorphine or diacetylmorphine or dihydrocodeine or	
	hydromorphone or opium tincture or tincture of opium or methadol or methadyl or	
	levomethadyl or naltrexone).tw.	
29	exp Opioid-Related Disorders/	26751
30	27 or 28 or 29	190647
31	26 and 30	5213
32	adolescent/ or child/	2809706
33	(adolescent* or child* or youth or young).mp.	4140604
34	32 or 33	4140604
35	31 and 34	862

In addition to peer-reviewed literature, the grey literature was searched for additional guidelines and reports. Documents within the grey literature are often produced by organizations such as government and inter-governmental agencies, non-governmental organisations, and industry, to store information and report on activities. The information published is often meant for wider sharing and distribution and published without the delays and restrictions of commercial and academic publishing. To that effect, clinical practice guidelines from medical organizations, professional associations, government agencies in over 30 identified countries were searched, paying close attention to website sections with names like "Documents", "Reports", and "Library".

The countries were selected based on the SUD treatment system, dictated by data published by the UNODC. Countries who reported on the coverage of treatment interventions (including pharmacological, psychosocial and rehabilitation and aftercare services) for SUDs (UNODC Indicator 3.5.1) were deemed most likely to have guidelines for the treatment of OUD in youth (187,188). Over the period 2015-2017, data on this indicator were reported to the UNODC by 29 countries. Those countries included Afghanistan, Albania, Austria, Bahamas, Bulgaria, Chile,

Croatia, Cyprus, Czechia, France, Germany, Greece, India, Italy, Latvia, Lithuania, Luxembourg, Malaysia, Malta, Mexico, Nigeria, Portugal, Romania, Singapore, Slovenia, Spain, Sri Lanka, United States of America, Uzbekistan. Moreover, a number of countries who were not listed above, such as Australia, New Zealand, Netherlands, Switzerland, and Canada, were also searched due to their extensive academic and medical involvement in the treatment of SUD.

3.3. Results

In this rapid review, the grey literature from 34 countries as well as 862 peer-reviewed articles were screened for youth specific guidelines. Only three countries (Canada, the United States, India) had specific guidelines dedicated to the treatment of opioid dependence among youth. A handful of other countries had short sections within the main guidelines for the general population on the specific treatment approaches for youth. As for the vast majority of countries, no clinical guidance documents for youth were found. In some countries such as the Netherlands, Mexico, Singapore, Luxembourg, and Latvia, there were a varying degree of available resources that youth themselves can access if they use substances, but there were no signs of explicit evidence-based clinical guidance documents in the literature.

3.3.1. Identified youth-specific guidelines

3.3.1.1. Canada

The informal clinical care guidance entitled "Treatment of Opioid Use Disorder in Youth" published by the *British Columbia Centre for Substance Use* (BCCSU) is a supplement to the clinical care guidance publication on the clinical management of OUD in adults and provides an overview of care principles and recommended treatment options for youth (96,189). The BCCSU guideline for youth recommends that the full range of available treatments be considered for youth with OUD, including OAT. It recommends that effective treatment plans for youth with moderate to severe OUD should be long-term and include a combination of psychosocial interventions, supports, and pharmacological treatments. Moreover, it recommends buprenorphine/naloxone as first-line treatment of moderate to severe OUD, which is in line with clinical care guidance for adults. Nationally, the *Canadian Research Institute in Substance Misuse* (CRISM) has published "National Guideline for the Clinical Management of Opioid Use Disorder" which is intended to guide treatment for the general population. Within this document,

the consensus of the guideline review committee suggest that the recommendations are equally relevant and applicable for specific populations such as adolescents and young adults (97).

3.3.1.2. United States

The policy statement entitled "Medication-Assisted Treatment of Adolescents with Opioid Use Disorder" made by the *American Academy of Pediatrics* (AAP) lists 3 major recommendations (74). In general, it recommends pediatricians to consider offering medication-assisted treatment to their adolescent and young adult patients with severe OUD. It also acknowledges that confusion, stigma, and limited resources severely restrict access to medication-assisted treatment of youth with OUD. Being a policy statement, it also advocates for more research and increased resources towards developmentally appropriate SUD treatment, including prevention, behavioral interventions, and medication treatment. In addition, the "National Practice Guideline for the Treatment of Opioid use Disorder" published by the *American Society of Addiction Medicine* (ASAM) have a section on special populations including adolescents (98,99). These are in line with the AAP statement, encouraging the use of the full range of treatment options, but also stating that federal laws and FDA approvals should be considered when recommending pharmacotherapy for adolescent patients (98,99). The guidelines also state that efficacy studies for these medications have largely been conducted in adults, and that there is virtually no data comparing the relative effectiveness of these treatments in adolescents (98).

3.3.1.3. India

An Indian resource published in the *Indian Journal of Psychiatry* provides clinical practice guidelines on assessment and management of substance use disorder in children and adolescents. These guidelines provide substance-specific recommendations for alcohol, cannabis, inhalants, tobacco, opioids, stimulants, and sedatives/hypnotics. For youth with OUD, the guidelines mention that, despite the increasing trends toward use of opioids in Indian adolescents, youth still do not receive adequate treatment due to restrictions on use of pharmacotherapy in this age group. The guidelines mention that OAT is the treatment of choice for adults and that buprenorphine and methadone should be used in children and adolescents with OUD, albeit with caution considering poor tolerability (190).

3.3.2. Sections within adult guidelines

In a handful of other countries, such as Australia, New Zealand, Malaysia, United Kingdom, and Sweden, no specific clinical guidelines for youth were found. Instead, there were sections within the general guidelines for adults dedicated to youth. For instance, in the "New Zealand Practice Guidelines for Opioid Substitution Treatment" from 2014, a section is written on opioid substitution treatment for clients under 18 (191). In it, they recommend youth receive the same level of treatment offered to adults following the principles outlined in the document, but be managed through specific youth addiction or mental health services (191). Similarly, in Australia, a subchapter within the "National Guidelines for Medication-Assisted Treatment of Opioid Dependence" is written on treatment approaches for adolescents, in which they place emphasis on psychosocial responses, harm reduction and family intervention approaches, with available substitution treatment after careful assessment (192). In the Australian province of New South Whales, a clinical framework exists which provides clear principles to health services working with young people with substance use concerns (193). However, due to the limited research on the use of pharmacotherapies with adolescents, this framework refers readers back to the adult guidelines on the treatment of opioid dependence, which includes a short section on the treatment of young people (194).

3.4. Discussion

We found shortcomings in the international body of clinical guidelines for the treatment of OUD in youth. There is an overall lack of evidence-informed guidance for high-risk opioid use among adolescents and young adults. Only a minority of countries have treatment guidelines, some of which are extremely short and outdated. As guidelines offer a way of bridging the gap between policy, best practice, and clinical context, the dearth of such an essential part to quality medical practice is a reflection of the political and clinical reality of substance use treatment for youth (195). From the clinical practice guidelines that were found, all encouraged youth to be offered the full range of evidence-based options, including pharmacotherapy. These are the same suggestions for adults, but in clinical practice, there are stark differences in the treatment philosophies for youth and for adults. Of individuals needing substance use treatment in 2017, 8.5% of adolescents aged 12 to 17 and 8.8% of young adults aged 18 to 25 received substance use treatment at a specialty facility, compared to 13.8% of adults aged 26 or older (196). The

lack of education, the endless formalities, as well as the stigma surrounding adolescent substance use has created a lack of preparedness in using pharmacotherapies for youth and a hesitance among many/most clinicians as well as parents/caregivers in providing OAT.

Medicine is not only driven by evidence but also political biases and ideological narratives. For instance, abstinence from sexual intercourse represents an idealized choice for teenagers, as it reduces their risk of experiencing unintended pregnancy and contracting sexually transmitted infections, including HIV/AIDS (197). However, abstinence-only education programs, although fully protective against pregnancy and disease in theory, often fail in actual practice because abstinence is not maintained (198,199). To that effect, comprehensive reproductive health promotion programs that provide information about contraceptive options and protection from STIs have been much more successful (200). With regards to substance use disorder, most youth will receive behavioural health services if they are to receive any treatment at all (84). Some prescribing barriers and policies actually require youth to attempt a trial of behavioral treatment alone before being provided with medication-assisted treatment (201). This model of addiction for youth still revolves around the idealistic perception that substance dependence is just a phase in development, rather than a chronic medical condition (202,203). Such beliefs, despite being in opposition to clinical practice guidelines and clinical trial data, argue that youth with high-risk substance use require brief behavioural interventions rather than long-term treatment with medication. Preconceived notions, misunderstandings and stigma surrounding long-term treatment with medication are damaging to any individuals but especially to youth since parents or guardians have the legal right to override the child and adolescent's decisions (204). Forcing a treatment trajectory such as abstinence on an individual that is not ready can be counterproductive. As suggested by the guidelines, youth should be offered the full range of treatments but instrumental to this is the voice of the youth in the decision-making process. For instance, though abstinence is desired and the end-goal for a lot of patients, the decision to begin tapering off of OAT should be shared and treatment duration should be prolonged for as long as the patient wishes (87,110,111).

This stigma associated with medication treatment for youth among patients, families and clinicians has been a major barrier to the expanded access and provision of pharmacotherapy.

Misconceptions surrounding medication treatment for youth, such as requiring it for the rest of their life, not really being in recovery, or simply replacing one addiction with another, has hampered the availability and distribution of pharmacological strategies (201,205). Without robust education, including but not limited to the development of good clinical practice guidelines, abstinence-based approaches will continue to be the mainstay in the treatment of youth. Pathways to OAT treatment should be more readily offered in pediatric primary care (181). There is the need to train pediatricians, family physicians, primary care providers for this specific population. It is necessary to inform and build capacity in primary care in order to better support patients and thereby reduce the stigma they may experience in specialized substance dependence clinics. Training should emphasize the psychosocial needs of youth and aim to develop a network of pediatric and family medicine practices as a collaborating circle of care (128).

3.4.1. Additional documents and resources

To add to the literature found through the rapid review search and to broaden its scope, a dozen of international colleagues from Europe, New Zealand and Australia specializing in the field of adolescent substance use were contacted in order to determine the level of clinical guidance surrounding high-risk substance use in youth in their respective countries. Their insights aligned with the principal finding of the rapid review, being that nothing or not much has been published on the topic. However, several additional publications were mentioned in communications which had not been included in this review as they did not fit the inclusion/exclusion criteria. As these are relevant to the discussion, they have been briefly described below.

Colleagues in Austria distributed a publication written in German that provides clinical guidance on OAT with youth entitled "Austrian model of opioid substitution for minors" (206). Colleagues in New Zealand shared a resource aimed at increasing the knowledge and confidence of those working alongside young people in the primary care environment to address issues related to alcohol and other substance use; this resource does not provide clinical guidance in the treatment of high-risk substance use (1). Another New Zealand resource was the SACS Brief Intervention (SACSBI), a method designed to deliver brief addiction treatment in a range of youth health and social services, and used by a wide range of NZ youth agencies (207). Three books were brought to our attention as well. The first is called "A Clinician's Guide to Treating Adolescent Substance Use" and aimed at increasing clinician awareness by discussing prevalence of substance use, prevention strategies, available screening methods and practical treatment applications (208). The second called "Adolescent Substance Abuse: Evidence-Based Approaches to Prevention and Treatment" focuses on adolescent substance abuse treatment, covering every aspect in detail (209). The third called "The Handbook of Systematic Family Therapy" includes a chapter on systemic approaches to adolescent substance abuse, which provides a short overview of evidence-based approaches to substance use interventions, especially in the context of family, parents, siblings and peers engagement (210).

These resources and documents, though not clinical practice guidelines, have the benefit of empowering young patients and their families to make more informed healthcare choices, and to consider their personal needs and preferences in selecting the best option. Additionally, lay versions of guidelines, books, and specific briefs, can benefit healthcare professionals caring for young patients by reinforcing appropriate practice with proven scientific evidence and improving the efficiency of care.

3.4.1. Limitations

By virtue of its design as a rapid review, this section is subject to some limitations. Firstly, most of the findings were published outside of bibliographic databases, possibly because the search strategy was specific to peer-reviewed publications listed only in Ovid MEDLINE and Ovid EMBASE. Moreover, the review only included publications written in English, potentially excluding relevant guidelines from non-English speaking governing bodies and medical associations. Future studies should include more bibliographic databased and include guidelines from a greater range of languages. Finally, this review is limited by its cross-sectional nature. We acknowledge and appreciate that more publications and guidelines have emerged since it's conception, such as a position paper on "Medication for Adolescents and Young Adults With Opioid Use Disorder" published by *The Society for Adolescent Health and Medicine* and a review on "Interventions for Alcohol and Drug Use Disorders in Young People" published in

Current Psychiatry Reports (201,211). This rapid review can act as a foundation for future research to evaluate temporal changes in the quantity and quality of clinical guidelines.

3.4.2. Conclusion

Medicine is not only driven by evidence but also by political biases like prohibition and abstinence. Moreover, dominant models of disease create another barrier, especially through stigma of specific behaviors such as substance dependence in youth. The lack of good clinical practice guidelines highlighted by this rapid review is a reflection of the gaps between policy, research and clinical practice in this domain. High-risk substance use has been identified as an international challenge but is not getting enough attention. Good clinical practice guidelines that promote interventions of proven benefit and discourage ineffective ones have the potential to improve consistency of care and quality of life as well as reduce morbidity and mortality. The dearth of clinical practice guidelines reaffirms the system failure of addressing the mental health and substance use needs of youth, and exposes the many gaps within the field of addiction psychiatry and adolescent medicine.

The next section will aim to create up-to-date and evidence-based consensus statements devised by clinicians and researchers in the field of youth adolescent substance use disorders in order to address the aforementioned gaps in research and practice, and to create common ground for future projects internationally.

4. International consensus

4.1. Introduction

The lack of youth-focused substance use treatment guidelines represents a missed opportunity to educate treatment systems, prioritize prevention and early intervention, and promote access to appropriate treatment resources. The objective of this third section is to explore the international context surrounding youth and substance use treatment with a panel of clinicians and researchers in order to identify key components on the therapeutic continuum for high-risk substance use in adolescence and early adulthood.

4.1.1. Background

The time between the ages of 15 and 24 is a very sensitive developmental period. This is a time of transition between childhood and adulthood, where both adolescents and young adults are often collectively labeled as youth (212). Large-scale developmental changes that are characteristic for this period make youth particularly vulnerable to mental health problems, high-risk substance use, and self-harm (6,9,11,213).

The most common reasons for mortality among adolescents and young adults (collectively referred to as youth) are unintentional injuries (mainly overdose and motor vehicle accidents) and suicide (31,32). In the context of the opioid overdose crisis, noticeable changes in life expectancy have been reported in Canada and the United States, which have been largely attributable to drug overdoses among young individuals (214,215). Moreover, the COVID-19 pandemic has further increased the risk of developing or worsening of mental and substance use disorders due to uncertainty regarding academics, careers, and social life amongst other concerns (216,217). Now more than ever, there is an obvious need to reduce the overall burden of disease and risk of premature death that is associated with mental health and substance use disorders among young people (28).

Yet, youth are much less able to access treatment for substance use disorder compared to adults, and treatment options offered to youth are substantially different than those offered to adults (218). Behavioural interventions without medication are the mainstay for treatment of substance use disorder among youth, despite guidelines recommending the use of pharmacotherapy in

young patients (74,178,189). For opioid use disorder (OUD) for example, clinical trial data and high-quality observational studies broadly support the use of medications such as buprenorphine, methadone, and naltrexone, which are associated with reduced overdose and opioid-related morbidity when compared with other treatment pathways such as no treatment and behavioral interventions alone (111,179,219–221). Yet, among youth who experienced a nonfatal opioid overdose, only 2% received pharmacotherapy within 30 days of overdosing and 29% received behavioral health services alone; more than 70% received no addiction treatment (84).

Unfamiliarity and stigma surrounding adolescent substance use has created a lack of preparedness in using a wide range of evidence-based treatment options. Many providers view opioid agonist treatment (OAT) as a 'last resort' for youth with OUD, often waiting until youth have relapsed or until they have experienced severe adverse consequences from other forms of treatment (180,181,205). If treatment offered is not engaging and retention is low, the patients are often blamed for a lack of motivation. Similarly, harm reduction services rarely accommodate the needs of adolescents, and are seldom used by youth, which further increases the risk of death (222,223).

The lack of comprehensive youth-focused substance use treatment guidelines represents a missed opportunity. Prioritizing prevention and early intervention, and promoting access to appropriate treatment resources are the best strategies to reduce overdose, as is done in parts of Europe such as Switzerland and Austria for example (206,224). A policy statement recently published by *The Society for Adolescent Health and Medicine* advocates for improving the receipt of medications for OUD among adolescents and young adults by addressing health system barriers, workforce limitations, and stigma, among other strategies (201).

4.1.2. Objective

The main objectives of this study are to source best practices from an international panel of experts and establish consensus for the screening, treatment, and management of high-risk substance use in adolescence and early adulthood, with the intention of improving the consistency of care for individuals below the age of 25 years.

Within the confines of this thesis, an international agreement on the prevention, treatment, and management of high-risk substance use among youth will create a universal platform for clinicians, researchers, and healthcare systems, which will help shift the paradigm surrounding substance use among youth, inform evidence-based clinical practice, and provide the basis for future research.

4.2. Methods

A modified Delphi process was conducted according to the steps described below and as shown in Figure 4.1. This study received approval from the University of British Columbia's Behavioural Research Ethics Board (H20-03464). Responses were collected electronically through a UBC-hosted version of Qualtrics.





Legend: A final international consensus was developed after a narrative review was used to create a semi-structured questionnaire, which was distributed to a panel of 31 experts. Responses to the semi-structured questionnaire were used to create initial statements. The statements then underwent 3 rounds of rating to reach consensus.

4.2.1. Panel Selection

A multidisciplinary international group of 35 experts were invited to participate in the consensus process. However, unlike the International Collaboration on ADHD and Substance Abuse (ICASA), there is no known international network for research and physicians on high-risk substance use and SUD among youth (225). Invitees were therefore identified through purposive sampling as distinguished clinicians and researchers in the field of youth SUDs, able to provide insight from their in-depth direct experience in working with adolescents. To be considered 'panelists', invited individuals had to have participated in at least one of the steps in the Delphi process, including the semi-structured questionnaire, any of the 3 rounds of rating, and the webinar. Of the 35 invited experts, 31 participated in the Delphi process, hereafter referred to as "panelists". The panelists were from 10 countries: Australia (2), Austria (5), Canada (6), Egypt (1), Germany (3), Italy (1), the Netherlands (2), New Zealand (2), Switzerland (6), United States (3). Within the panel, there were 21 psychiatrists (including 13 addiction psychiatry specialists, 4 child and adolescent psychiatry specialists, 5 dual specialists in addiction psychiatry and child and adolescent psychiatry), 4 pediatricians (including 2 adolescent medicine specialists, 1 dual specialist in adolescent medicine and addiction medicine, and 1 dual specialist in developmentalbehavioural pediatrics and addiction medicine), 3 psychologists (including 1 youth addiction specialist, 1 addiction medicine specialist, and 1 mental health and addiction specialist), 2 general practitioners (including 1 addiction medicine specialist and 1 psychosomatic medicine and psychotherapy specialist), and 1 emergency medicine physician.

4.2.2. Semi-structured questionnaire

The first step of the Delphi process was meant to gather information by using a semi-structured questionnaire. The instrument was initially developed based on the published narrative review described in Chapter 2, as well as on the rapid review described in Chapter 3. Based on these reviews and clinical expertise, open-ended questions were constructed and organized into six domains with corresponding actionable goals:

A. Clinical risks (11 questions): outlining clinical risks of substance use and of developing of substance use disorder in youth in the clinical trajectory, in order to provide a more

appropriate form of clinical risk assessment so as to enable clinicians to select more effective and engaging interventions.

- B. Target populations (2 questions): determining target populations in the prevention and treatment of youth using psychotropic substances to prevent severe adverse events and their specific needs for intervention.
- C. Intervention goals (10 questions): defining acceptable and engaging treatment goals for adolescent users in order to best address their needs and help in their recovery.
- D. Evidence-based strategies (12 questions): exploring experiences with evidence-based intervention strategies in the current systems of care for adolescents using psychotropic substances, in order to identify which evidence-based strategies help patients understand risks of substance use and how to manage risk factors, prevent defined risks from leading to severe adverse events, support the development of coping skills, and support recovery.
- E. Treatment settings and expertise (5 questions): identify the medical disciplines that should have the responsibility of coordinating and innovating this area, as well as the other disciplines need to be involved.
- F. Case stories (optional): share and document the current situation internationally in order to be able to compare experiences across health care systems and standardize reporting as an important tool in addition to epidemiological reviews

The final version of the semi-structure questionnaire included 40 questions (Appendix A). The questionnaire was sent to the multidisciplinary international panel of 31 experts. Based on the responses collected from the semi-structured questionnaire, 63 initial statements were generated. These initial statements, designed by the primary authors, were meant to encapsulate the responses provided by the panelists. In some instances, statements were created from panelists' responses verbatim, while others were slightly modified to ensure that the spirit of all responses were coherent with the statement.

4.2.3. External Feedback

The study design, semi-structured questionnaire and initial statements were presented in a workshop at an international conference (*High-Risk Substance use and Overdose Among Youth Conference*) on January 25th, 2021. The attendees of the workshop (roughly 80 individuals

representing healthcare professionals, social services workers, counsellors, researchers, policy makers, etc.) had the opportunity to comment and provide feedback, as well as discuss the context and impact of such statements. Some initial statements were revised based on the external feedback provided by the attendees and discussions had during the workshop.

4.2.4. Consensus Building

Based on the responses to the semi-structured questionnaire and external feedback during the workshop, all statements were sent to the panelists who were asked to rate all statements on a scale of 1-5 (1 = strongly disagree, 2 = somewhat disagree, 3 = neutral, 4 = somewhat agree, 5 = strongly agree) based on their knowledge and clinical experience. If panelists disagreed with a statement, they were given the opportunity to provide comments on the content and/or the phrasing of the statement. Panelists were also given the opportunity to propose any additional statements they felt would be useful.

After all ratings were received, consensus was calculated. Consensus for each statement was defined as at least 95% of all ratings being greater than or equal to three ("strongly agree", "somewhat agree", and "neutral"). For example, if 24 of the 31 panelists responded, a statement would not reach consensus if less than 95% of 24 (22.8) disagreed with the statement ("strongly disagree" and "somewhat disagree"), which means that the statement would reach consensus if no more than one expert disagreed with the statement. This same procedure has been used in recent published consensus statements, in which "neutral" ratings in a dichotomous consensus measure have been understood to reflect at least some agreement, rather than disagreement (226,227). All statements without consensus were revised based on comments and suggestions provided by the panelists.

These revised statements were sent out for a second round of rating along with any additional statements proposed by the panelists. Consensus was calculated for this subgroup of statements using the same a priori defined rules. Statements that still did not reach expert consensus were deemed controversial and were discussed with the panel during an online webinar.

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4.2.5. Internal Webinar

A webinar was organized with all the panelists on the March 31st at 11 am PST. The webinar was an hour in length and organized as follows: summary of results, discussion of identified areas of disagreement, revision of statements that did not reach consensus, and discussion on next steps and priorities. A short presentation provided an overview of the project thus far, which was followed by a discussion moderated by Dr. Krausz. Panelists were encouraged to use evidence-based arguments instead of faith-based, and provide support from the literature when needed. All statements discussed in the webinar were revised based on the comments made by the panelists.

4.2.6. Consensus Completion

These revised statements were sent out for a third round of rating. Consensus was calculated for this subgroup of statements using the same a priori defined rules. The full text of the international consensus statement was prepared and shared with the panelists, with an opportunity to comment and provide feedback on the text. Based on the final round of feedback and comments from the panel, the international consensus statement document was finalized.

4.2.7. Terminology

Throughout each step of the Delphi study, the following terminology was used by the panel, defined as follows. The term "youth" was broadly defined as the developmental period which begins with changes of puberty and culminates in the assumption of adult roles, generally defined as between 10 and 24 years of age (228–230). The term "youth" encompasses both adolescents (10-19 years old) and young adults (20-24 years old), but it is nevertheless important to recognize the different challenges and needs of the two subpopulations in the prevention, treatment, and management of high-risk substance use. The panel believes that it makes sense to talk about them collectively as "youth" or separately as "adolescents" and "young adults" when appropriate (231). Moreover, high-risk substance use was defined as any use of substances with a high risk of adverse outcomes (i.e., physical injury, mental health and substance use disorder development, criminal justice involvement, school dropout, loss of life), and includes misuse of prescription drugs, legal substances, use of illicit drugs, and use of injection drugs (232).

4.3. Results

The results of the Delphi process are divided into three sections: International Youth Consensus Statement, International Overdose Situation, Case Stories (Figure 4.2). The first part reports on the stepwise and quantitative approach taken in producing the international consensus statement, whereas the second and third part illustrate the qualitative responses of panelists to questions regarding the overdose situation in their respective country. Given the comprehensiveness of the project, especially the semi-structure questionnaire, a wealth of information was provided by panelists, not only in relation to best practice recommendations for the treatment of high-risk substance use in youth, but also with regards to the context in specific countries, thereby resulting in a more complete picture of youth substance use globally.





Legend: The results of the Delphi Process can be divided into three sections: 1) the International Youth Consensus Statement, based on the expert agreement on best practice and recommendations; 2) the International Overdose Situation, based on the subjective description of the overdose situation by panelists; 3) Clinical Case Presentations, based on descriptive and illustrative case stories by panelists.

4.3.1. International Youth Consensus Statement

4.3.1.1. Semi-structured questionnaire

The semi-structured questionnaire asked each panelist to share their views on the principles of prevention, treatment, and management of high-risk substance use in youth (Appendix A). Of the 31 panelists, 19 responded to the semi-structure questionnaire (61.3%). A total of 63 initial statements were generated from responses, and subsequently revised based on feedback received

during the international workshop. These 63 statements provided structure for the first round of rating.

4.3.1.2. First round of rating

A questionnaire was developed based on the 63 initial statements using an online survey platform (Qualtrics). Of the 31 panelists, 24 participated in the first round of rating (77.4%). Roughly half of the statements reached consensus (28; 44.4%). Of the remaining 35 statements, 18 were revised for another round of rating, while 17 were removed due to redundancy or repetition. In addition, 14 new statements were created based on suggestions provided by the panelists. The 18 revised statements and the 14 new statements provided structure for the second round of rating.

4.3.1.3. Second round of rating

Of the 31 panelists, 24 participated in the second round of rating (77.4%). Of the 32 statements distributed, half reached consensus (16; 50.0%), while 14 were revised and two were removed; six new statements were created. The 14 revised statements and six new statements were used to fuel the discussions in the webinar.

4.3.1.4. Webinar

Fifteen panelists attended the online webinar (48.4%). Five major topics were presented to the panelists which had been controversial in the previous rounds of rating: mental health and substance use screening (two statements), goals of treatment (two statements), involuntary admission (one statement), first-line treatments (five statements), family involvement (three statements). Based on suggestions made by panelists in the webinar, the 20 statements were revised for the third round of rating

4.3.1.5. Third round of rating

Of the 31 panelists, 22 participated in the third round of rating (71.0%). Of the 20 statements distributed, 16 reached consensus and four were removed. Of note, the statement on involuntary admission, which had been a major topic of discussion in the webinar, did not reach consensus in third round.

4.3.1.6. Finalization

In summary, consensus was reached on 28 of the 63 statements in the first round of rating, 16 of the 32 statements in the second round of rating, and 16 of the 20 in the third round of rating, resulting in consensus for 60 statements (Table 4.1). Of the 31 panelists, 17 participated in all three rounds of rating, four participated in two of the three rounds, and nine participated in one of the three rounds. Only one panelist did not participate in a round of rating but responded to the semi-structured questionnaire.

The agreement reached in this panel provides a direction to strengthen the system towards a structured and comprehensive approach, reflected in future guidelines and health care system development. Ideally, it will help to initiate a discussion on capacity building in all mentioned domains.

- A. Clinical risk/concurrent conditions: screening for mental health problems, substance use problems, and related risks is recommended for all youth. Beyond this, critical context such as family history, social network, early trauma, psychiatric comorbidities, physical health, housing situation, employment status, and resilience are important to explore in a conducive therapeutic setting.
- B. Target populations: it is recommended that specific preventative and therapeutic needs be addressed in the treatment trajectories of vulnerable target populations (e.g., marginalized environments, concurrent conditions, complex familial/social environments, pregnancy), and that this be integrated into specific existing services and youth-tailored services.
- C. Intervention goals: principal and guiding objectives in treatment are risk reduction and mortality reduction, as well as increasing resilience and positive development. It is important this happen as early as possible (learning from experiences with first episode programs in the treatment of schizophrenia) and be based on skill training and accessible resources (e.g., web-based care as first line of contact).
- D. Evidence-based intervention strategies: it is recommended that all evidence-based interventions be made available to youth, including targeted prevention, early intervention, and especially pharmacotherapy as first-line treatment for opioid and

benzodiazepine dependence. Family involvement is often recommended and could happen in different ways, considering the specific experiences of the individual youth.

E. Appropriate treatment settings and expertise: it is recommended that all treatment settings and professional teams be empowered through specialty-appropriate education and training for proper referral or management of high-risk substance use among youth.

Table 4.1 Consensus statements on the prevention, management, and treatment of high-risk substance use among youth

<i>A. C</i>	linical risks/concurrent conditions
1	Screening for mental health problems, substance use problems, and related risks in
	primary care and other clinical settings is recommended for all youth.
	(without the parent(s)/ caretaker being present), and it is important for discussions
2	surrounding mental challenges, substance use and related risks to be done in an open and
	non-judgmental way.
2	It is recommended that youth who are known to be at risk of SUD due to mental health problems or family history of SUD and montal health receive targeted prevention afforts
3	and more frequent screening.
	It is recommended that other critical domains be assessed among youth with high-risk
1	substance use when deemed appropriate by primary care providers. These can include
4	functioning, high-risk behaviors, physical health, housing and financial situation
	employment and academic capacity, coping strategies and resilience.
	It is recommended that trauma be carefully and methodically assessed among youth with
5	high-risk substance use by providers that youth can trust and feel comfortable sharing with
	Among youth with high-risk substance use, it is recommended that psychiatric
6	assessments for mental health and substance use disorders be done routinely using
	clinical guidelines for screening and assessment of mental health.
	Among youth with high-risk substance use, it is recommended that physical health
7	complications be done routinely using clinical guidelines for screening and assessment
	of physical health.
	Among youth with high-risk substance use presenting with first episode of psychosis, it
8	is important to rule out transient causes of psychosis such as substance-use or medical ailments. Youth must also be assessed for primary psychotic disorders
	Youth with high-risk substance use presenting with severe infections such as Hepatitis C
9	and HIV must be offered treatment according to guidelines and be provided with best
	guidance to make an informed decision.
10	It is recommended that protocols be in place for any youth who experience serious life-
10	unreatening outcomes such as overdose, consecutive binge drinking episodes, strong suicidal ideation
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	Protocols for youth who experience serious life-threatening outcomes should
11	recommend that youth be provided with immediate access to counselling, case
11	management, appropriate pharmacotherapy treatment, and the encouragement to notify
	and involve social support systems.
<i>B. Tc</i>	arget populations
1	Services must be tailored to the developmental age of the individual and be substance-
1	specific, severity-specific, and risk-specific.
	Having parents with SUD is one of the most prominent risk factors for youth to develop
2	SUD in adolescence and/or early adulthood; prevention and early identification are
	paramount for youth whose parents suffer from SUD.
	It is important that parents with SUD be supported in maintaining guardianship and
3	provided with parenting guidance when appropriate; treatment should work towards
	stabilizing the family as a unit.
4	For youth whose parents suffer from SUD, special attention should be paid to the youth's
	experiences and their relationship with their family members.
	It is recommended that substance use and mental health care organisations routinely ask
_	parents with SUD about family functionality to ensure the needs of the youth are being
5	addressed. Protocols should be in place to notify specialized organizations and
	appropriate government ministries if there is suspicion of child abuse and family
6	It is recommended that youth with high-risk substance use and living in marginalized
0	environments be provided supportive nousing options in cooperation with engaged
	Institutions (youth wehare services, treatment services, narm reduction services, etc.)
7	It is recommended that young remaines of childbearing age who are at risk of becoming
/	acumselling, and sexual health assessments as appropriate
	It is recommended that young females using substances who are expectent methors be
	revided with access to supports that specifically address their needs including prenatal
8	and postnatal care services health education and consulting services as well as family
	nlanning services
	It is recommended that young females using substances who are expectant mothers be
	provided supports to help develop their capacity as a caregiver, and should be connected
9	to services to address risks and encourage parenting. Foster care, adoption, and
-	termination of pregnancy can also be options if desired by the expectant mother, and
	resources for each option should be available.
1.0	It is recommended that youth with concurrent conditions be specifically engaged with
10	multidisciplinary teams specializing in dual diagnosis among youth.
	It is recommended that youth with concurrent conditions be specifically offered
11	psychoeducational activities for improving awareness about the triggering effect of
	substances and the worsening of psychiatric conditions.
	It is recommended that youth with opioid use or regular stimulant use be provided with
	age-appropriate counselling, case management, family therapy, and pharmacotherapy,
12	ideally all through the same treatment program for integrated care. Peer support, harm
	reduction services, selected preventive interventions, and health education, should also
	be provided.
C. In	tervention goals

	The objectives in treating youth with high-risk substance use are to reduce harm and
1	mortality, provent interference in adelescent development and substance related
1	impairment, and promote resilience and positive youth development
	SUD treatment should be goal oriented tailored to each individual and provided in
2	SOD treatment should be goal-oriented, tanored to each individual, and provided in
	partnership with youth and others collaborating in their care
2	It is recommended that all evidence-based interventions be available, and used according
3	to the needs and preferences of the patient in collaboration with the care team for
	maximal engagement.
	Relapse is part of the symptomatology. Youth must be enabled to recognize what to do
4	when the risk of relapse is high, or when a slip has occurred. Motivation interviewing,
	skills building, and mitigating risks of substance use are recommended to help attain
	goals.
_	It is important to discuss overdose in an open and direct way within a harm reduction
5	framework. Youth who (intend to) use drugs should have access to a spectrum of youth-
	friendly harm reduction services and be encouraged to use them.
6	It is important to provide Naloxone/Narcan and education to the entire community
0	surrounding a youth with high-risk substance use, including their family and friends.
	It is recommended to warn youth prescribed opioids for pain management about the risks
7	of substance misuse/overdose and be assessed frequently for step down to appropriate
	medications, as directed by specific guidelines for clinicians.
	If necessary, youth prescribed opioids for pain management and at high risk of
8	prescription opioid misuse and/or opioid dependence should be given Naloxone/Narcan
	and offered resources for prevention and treatment.
	It is important for psychoeducation and risk management to be accessible in schools, in
9	health systems, in vocational activities, in mainstream media, through online
	interventions and open discussions with the caring adults in their lives.
	It is important for standard school-based programs to be provided as part of the
10	curriculum to reduce barriers, increase primary prevention, and target early intervention
	for youth who are at risk.
	It is important for all youth to have access to online tools for risk assessment and
11	monitoring, which can provide them with the opportunity for personalised feedback,
11	tailored information and harm-reduction advice rapidly, while also being anonymous if
	desired.
<i>D. E</i>	vidence-based intervention strategies
	It is recommended that psychosocial evidence-based intervention strategies including
	family therapy, motivational interviewing, counselling, cognitive behavioral therapy,
1	integrated treatment of concurrent disorders and peer support be offered to all youth with
	SUD.
	For opioid dependence, evidence-based medication treatments including opioid agonist
2	treatment (OAT) are recommended as the first-line intervention.
	It is important that the range of medications for onioid dependence (including
	buprenorphine, methadone, extended-release naltrexone, slow-release morphine, etc.) be
3	available to youth and that medication choice be prioritized based on the preference and
	needs of the patient.
<u> </u>	For high-risk cannabis use, behavioral interventions such as motivational interviewing
4	cognitive behavioral therapy and family therapy are recommended
	cognitive conditional morapy and raining morapy are recommended.
	For stimulant dependence, behavioral interventions such as contingency management.
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5	motivational interviewing cognitive behavioral therapy and family therapy are
	recommended Medication may be required to manage problematic symptoms
	narticularly in stimulant withdrawal
	For honzodiazoning dependence, it is recommended that nhormeesthereny involving the
6	For benzodiazepine dependence, it is recommended that pharmacotherapy involving the
	gradual tapering of benzodiazepines be considered as first choice treatment if there is
	chance of withdrawal. Regardless, behavioral interventions such as contingency
	management, cognitive behavioral therapy, and family therapy are also recommended
	along with symptomatic treatment.
7	As most new and established medications have not been systematically evaluated in
	young people, decisions about their use should be taken with reference to the evidence-
	base in adults or as evidence emerges in youth, and include a collaborative risk-benefit
	analysis.
8	It is recommended to assess youth for informed decision-making capacity and engaged
	in appropriate assent or consent processes when choosing the appropriate treatment
	options. Parents/caretakers should be involved to support decision-making and treatment
	when appropriate.
9	Text message reminders, contingency management, case management, community
	support, and motivational interviewing are also recommended to enhance adherence and
	retention.
10	Educating the public, addressing the stigma, easing transition between the services, and
	training providers are all paramount in increasing overall access to OAT
	Inpatient rehabilitation should be considered for youth with high-risk substance use if
11	this is the preference of the youth if the social environment is toxic, if the bousing
	situation is very unstable, if there is a long history of unsuccessful treatment attempts, or
	if there are severe negative medical social and psychological consequences to any other
	ontion
	Treatment approaches can be made developmentally appropriate by using language that
12	is accessible to youth by focusing on their cools, and by individualizing their treatment
	is accessible to youth, by focusing off their goals, and by individualizing their treatment
	trajectories to meet their specific needs through youth/provider joint decision-making.
13	It is recommended to involve parents/caretakers in the treatment process. Even in
	dystunctional families or in case of divorce, parents/caretakers remain a critical resource
	for recovery. Treatment or consultation can happen in different ways from direct family
	sessions to parallel consultations. However, limited or no parental involvement should
	not be a barrier to treatment for youth.
14	Family involvement can be counterproductive in certain situations such as significant
	family conflict, abusive relationships, violence and estrangement. It is important for
	youth protection to be prioritized.
15	Youth should guide who is involved in their treatment and this should be respected. It is
	critical to encourage effective autonomy while balancing that against capacity for
	effective health-directed decision making. Disclosure to others collaborating in their care
	should be done with careful consideration of the risks of mistrust and disengagement.
	However, if youth or others are at risk of significant harm, breach of confidentiality
	needs to be considered.
	If the parents/caretakers don't support treatment initially (often due to a
16	misunderstanding or preconceived notion), their involvement should continue to be
1	misulatisaliand of preconcerved notion, then involvement bhould continue to be

	encouraged via education, enhancing trust, and relieving concerns. It is important that	
	interventional strategies work with parents/caretakers and youth in parallel, until they	
	agree to have common sessions.	
E. Appropriate treatment settings and expertise		
1	Peer support and case managers are quintessential to all treatment settings, with seamless	
	transitioning and hand-off between all treatment settings.	
2	It is important for emergency department and intensive care admissions to act as a	
	touchpoint and gateway for screening, brief intervention, and referral to treatment. It is	
	recommended that youth be immediately linked to case-managers and offered a private	
	space for visits from caregivers. Youth should be referred to substance use treatment as	
	soon as possible and be connected to therapy depending on their preferences.	
3	All services including outreach and harm reduction must be low-threshold, youth-	
	friendly, and stigma-free. They have to be interesting and safe to youth.	
4	All services must have seamless transitions and referrals to treatment centers for youth	
	interested.	
5	Youth in adult treatment facilities often indicate feeling confronted by adult addiction	
	services and do not feel at ease.	
6	Easy transportation to and from services, flexible hours that work for youth and the	
	possibility of online interventions (texting, social media, apps) are recommended.	
7	Professionals must be empowered and feel comfortable dealing with high-risk substance	
	use among youth, no matter their specialization. The healthcare system as a whole must	
	be better trained in dealing with high-risk substance use among youth.	
8	It is important to provide physicians involved in the care of youth with specialty-	
	appropriate education and training for proper referral or management of high-risk	
	substance use among youth.	
9	There is an urgent need for more clinical research such as randomized controlled trials	
	and high-quality observational studies that focus on improving models of care for high-	
	risk substance use in adolescents and young adults. Explicit clinical research on high-	
	risk substance use among adolescents and young adults needs to become a priority.	
10	Critical data about serious adverse events among youth who use substances including	
	non-fatal and fatal overdose events as well as about treatment capacity (including	
	number of young patients dispensed OAT and number of youth OAT prescribers), must	
	be collected, analysed and reported in a timely fashion.	

4.3.2. International Overdose Situation

Given the number of countries represented in the Delphi study, a few questions within the semistructured questionnaire were not used in the consensus process but were rather meant to provide a 'live' insight into the reality of the overdose situation in each respective country, as reported by experts working in the field. Stark differences were reported, which are summarized below.

4.3.2.1. Current overdose situation

Experts from Canada reported significant harms related to the opioid overdose crisis including recurrent emergency visits, fatal and nonfatal overdoses, as well as significant increase in overdose among youth. Similarly, in the United States, experts mentioned that "Youth continue to die at high rates and often suffer recurrent overdoses. There is minimal treatment available for youth with OUD in the USA and many do not access treatment after their overdoses."

Conversely, among experts in countries such as Germany, New Zealand, Switzerland, the Netherlands, and Austria, all reported the relative absence of an opioid overdose crisis. To the following question "How has the overdose crisis effected youth in your country?", German experts simply responded "N/A". Similarly, Austrian experts responded: "We don't see such a crisis in Austria; overdose deaths have been stable for many years. " In New Zealand, experts reported that PWUD have minimal access to novel synthetic opiates which has helped minimize the number of overdose deaths. In Switzerland, experts reported that the most severe overdoses have been associated with benzodiazepines, while in the Netherlands, overdose incidents among youths are mainly attributable to alcohol, in what is referred to as 'coma drinking'. The Dutch panelists mentioned an upsurge in the use of prescribed opioids, in particular the use of Oxycodone, but cannot speak of an overdose crisis because the number of opioid overdose incidents are very low. In Egypt, the panelist spoke of Tramadol as the most commonly used substance among youth but that due to its low potency and low risk of overdose; overdose rates are low in Egypt.

4.3.2.2. Concerning developments

Experiences with high-risk substance use among youth are incredibly varied among different countries and regions. Generally, the most common development being reported across the world involves early consumption of cannabis and cannabinoid products as well as heavy alcohol consumption and binge drinking, progressing to benzodiazepine, stimulant, and opioid use (depending on the availability in each country) in late adolescences. The most concerning within this progression is the random and concurrent consumption of drugs with little or no knowledge about their effects or concerns about their risks. The riskiest development is the beginning of

opioid use, especially of intravenous use of heroin in combination with alcohol and benzodiazepine use.

In the United States, experts reported that "some of the most disheartening trends over the past 5-10 years have involved increasing use of highly concentrated cannabinoid products, with more kids presenting with psychosis. The vaping epidemic has also been extremely concerning and we have seen teens with new clinical presentations that we had not seen with cigarettes." In New Zealand, the most recent concerning trends involve synthetic stimulants sold as MDMA with a high potential for overdose. This is similar to what is reported by panelists in Austria and the Netherlands. The high use of 'party drugs' like GHB and MDMA, which are becoming more and more synthetic, are leading to more emergency admissions and are increasingly becoming the reason for admission to treatment. In Egypt, Tramadol use is increasing horrendously among adolescents in schools. Surprisingly, the rate of Tramadol use among females is also rising, which is a new trend due to the prevailing societal stigma surrounding female substance use in the Arabic culture. Aside from substance, experts also mentioned gaming and internet use as a recent emerging and concerning development, some going even as far as saying that "this will be the next biggest problem in the modern world."

4.3.2.3. OAT Coverage

Panelists were asked to report the prevalence of youth with high-risk opioid use in OAT programs, with 3 response options: "OAT is the normal available treatment option", "OAT is only used as exception" and "OAT is not recommended and not used". Quite generally, across all countries, panelists reported that the younger the patient, the less likely they are to get medication.

Panelists from New Zealand, the Netherlands, and Austria all listed OAT as the standard and conventional treatment option. However, there remain some country-specific differences. In Austria, youths are usually provided OAT by GPs, as it is for adult opioid users, and in cooperation with an adolescent psychiatrist. In the Netherlands, though it is the normal option, it is not used that widely due to the limited number of high-risk opioid using youth in the country. In the US and Canada, panelists reported that OAT was only used as an exception. One of the

main contributors to this multifactorial problem is that OAT is not available in many treatment centers, and that too few physicians feel comfortable prescribing it for this age group.

4.3.2.4. Addressing the needs of youth

Panelists were asked to outline the most important steps in addressing the needs of youth in their country. Common to all was the need for outreach and low threshold care to better screen for substance use early on. Moreover, maintaining and building well-functioning youth treatment facilities for high quality care which provide psychological services with pharmacotherapy were highlighted by most panelists. In the United States and Canada, addressing the stigma surrounding substance use in youth by educating the public and increasing youth-trained providers were also mentioned as important steps to take, along with more research of treatment interventions and development of guidelines. In Egypt, a country with minimal infrastructure in place for mental health for adults and quasi-nonexistent treatment services for youth, putting youth mental health as a priority along with having a paradigm shift to online interventions and e-mental health were cited as important steps.

4.3.3. Case Stories

Panelists were also provided with the opportunity to add a short case story to illustrate a clinical presentation. They were structured by first describing the individual's substance use history and mental health diagnosis, followed by the treatments provided. In total, 3 panelists provided case stories, summarized below (Appendix B).

4.3.3.1. Case story from Egypt

A 16-year-old male patient from Egypt was seen as an outpatient clinic for substance use disorder. He used tramadol, cannabis, and heroin, though tramadol was his substance of choice. He has overdosed once before, the details of which were not shared. He was also diagnosed with PTSD. He was pushed to seek treatment by his family members after having experienced a substance-induced manic episode. His previous treatment history includes symptomatic treatment and detoxification. After consultation with the outpatient clinic, he was treated with pharmacotherapy including benzodiazepines, NSAID, antidepressants, mood stabilizers, as well as psychosocial treatment including motivational interviewing, dialectical behavior therapy, and cognitive behavioural therapy.

4.3.3.2. Case story from the Netherlands

A 17-year-old male patient from the Netherlands was seen in an outpatient clinic. He primarily uses amphetamine, using as much of it as he can afford. He also uses cannabis daily and binges alcohol on weekends. He lived at home with his parents and 3 siblings, and mentioned having familiar problems. In his peer group, he mentioned that they also use drugs as well. The only adverse event he has ever experienced was ending up in the emergency department after polysubstance use, but no more information was shared. Upon presentation, the youth was diagnosed with MDD, PTSD, AHDH along with SUD. Previous treatment history included inpatient detoxification after failed attempts of outpatient care. ADHD medication was started but then quickly discontinued because the medication induced a craving for speed. Following detoxification, he stayed clean for 2 years but relapsed with cannabis. He is currently attending cognitive behavioural therapy for cannabis use, attending eye movement desensitization and reprocessing therapy for his PTSD, and taking AHDH medication.

4.3.3.3. Case story from the United States

A young adult patient (25 years old) was seen in an outpatient setting. His substance use included crack cocaine, heroin, cannabis, alcohol, with no history of overdose. Along with his SUDs, he was diagnosed with MDD. His treatment history includes residential treatment, which he has tried more than 8 times in the last 8 years. He is currently living in a recovery house and taking Sublocade for his OUD. This has been working well for him, as he has been abstinent from heroin but continued to use crack cocaine daily.

4.4. Discussion

4.4.1. International consensus

Globally, youth-tailored services for high-risk substance use are rare. Many treatment paradigms for high-risk substance use among youth are focused on abstinence without considering other goals. This is unlike treatment protocols for adults and is not based on clinical research evidence (74,111,123,180,195,201). To address this gap in clinical practice and treatment guidance, an

international consensus statement was developed for high-risk substance use among youth with a Delphi design based on a panel of experts.

A consensus process attempts to define common ground while acknowledging differences in opinions and perspectives, a necessary first step in addressing necessary reform and system development to achieve better health outcomes in youth, based on priorities. The next step would be the design and implementation of solutions according to the regional context of each healthcare system. Given the significant neglect of clinical research, healthcare capacity and quality of services, which have led to severe harm and death, a significant change is needed (84,205,233,234).

Areas of particular contention are in regard to screening for substance use and related risks. Though consensus was achieved, experts expressed concern in the feasibility of screening all youth due to the risk of labeling, stigmatizing and potentially inappropriately pathologizing youth. This reflects a broader debate within Adolescent Psychiatry of labeling and pathologizing adolescents and young adults, which may be deemed as inappropriate given their developmental stage (235–237). Moreover, selective screening means that providers can make assumptions about youth risks, which may contribute to disparities (racial, socioeconomic, etc.) (238,239). The screening of all youth for mental health problems, substance use problems, and related risks was also called into question from a feasibility standpoint, due to the many illnesses already screened for in primary healthcare, despite agreement among the experts regarding the need for such screening. To minimize the workload among primary care and mental health providers, the use of standardized tools, frameworks, and resources such as online screening and assessment platforms may be extremely useful (240,241). The screening should avoid adding more burden to already unbearable workload primary care physicians, rather develop a common focus on known risk factors screened with standardized online tools, given the significant impact of risk factors on health outcomes. An important example is early childhood trauma, a known risk factor for high-risk substance use and SUD (242–245). These screenings could be easily provided in the form of online tools and as part of an online platforms which also offer support and information (e.g. Climate Schools in Australia) (246–248). However, a broader evaluation of the healthcare

system as a whole is needed if screening for mental and substance use disorders, the leading cause of disability in children and youth, is unfeasible (28,249).

The only statement with no consensus concerned involuntary admission, a complex ethical issue in youth and still highly contentious in adults. Although most experts agreed that involuntary admission could be considered as part of a comprehensive treatment approach in extremely complex and high-risk situations, most experts also drew attention to the potential significant consequences it could have on the trust and engagement of patients. Recent literature has demonstrated that youth who are hospitalized involuntarily report more distrust, including perceiving inpatient treatment to be more punitive than therapeutic (169,250–252). A clear distinction should also be drawn between involuntary admission and involuntary treatment, the former of which is intended to interrupt a cycle with stabilization care. Nevertheless, the panel did not come to a consensus on an approach of this much weight and magnitude, without first gathering scientific evidence. Research is critical to quantify the risks and benefits of this approach and to evaluate the effects of this approach on the long-term health outcomes of youth. In reality, involuntary treatment is often used as the last resort in a crisis that has escalated due to mostly inappropriate treatments which came too late within a non-existent continuum of care to often. This discussion should focus on how to intervene early and engage the patients through meeting their needs. The innovative work done with young patients experiencing first-episode psychosis demonstrates the benefit of early intervention approaches, which contributed to a paradigm shift in the system of care with better health outcomes (253–256). A similar approach is warranted for traumatized youth with high-risk substance use, who have the highest rates of mortality among young mental health patients (31,32,257).

If we want to reduce high-risk substance use, substance use disorder prevalence, and overdose in young patients, we need evidence informing practice instead of personal beliefs and subjective preferences only. We need a continuum of care, from lifestyle mentoring and targeted prevention to early crisis response. A clinical trajectory addressing developmental, mental and physical challenges needs to be established. Services and resources (e.g., welfare, perinatal) must be tailored to the specific therapeutic needs of vulnerable young target populations. Family is also a major resource to involve an adolescent's treatment process, but should not be a barrier to care

(258). In the case of serious life-threatening events and emergency situations, such as nonfatal overdose or suicide attempts, a youth appropriate crisis response system needs to be established. Every youth waking up in an emergency room after a binge-drinking episode or an overdose should get the best possible care immediately. This includes a diverse range of available and effective treatment options such as counselling, case management, family involvement, and pharmacotherapy. Specifically, the amalgamation of evidence-based medications for opioid dependence must be offered, and exceptions to using specific mediations for OUD in youth need to be justified through clinical research that prove that the positive effects shown for adults are not to be expected among adolescents. Without more clinical research, innovation and new settings of care as part of health system development, the effective prevention, treatment, and management of high-risk substance use among youth is impossible.

Guidelines have no merit on their own without implementation. The first step to this important work would be to further understand country-specific adaptations due to differing culture, legislation and philosophies to care. This is particularly relevant when considering the issue of involuntary admission and treatment, as there are differences in its applicability in terms of legal and regulatory issues, particularly in young people. Guidelines need to be integrated into policies which clinicians should be incentivized to execute. Education, and emphasis of workplace culture is necessary in achieving these end outcomes. This can include continuing education, and specialized training in addiction and psychiatric care for non-specialized clinicians as well as promoting awareness in the institution. In designing the execution strategy, frontline providers and clinicians should be invited to take part in stakeholder meetings and included in reshaping care for youth with substance use and concurrent disorders. It is important that best practices are shared amongst providers around the world. An international platform or committee could be created for further consultation and guidance on this topic, similar to ICASA (225). Furthermore, to ensure guidelines are updated, clinical research capacity in this area is a necessary focus and continuous research is needed to ensure sustainability. There is a lack of well-conducted trials for this demographic which contributes to the lack of evidence to guide clinical care (178,179,219,259). More than in other areas, a transdisciplinary collaboration is necessary across sectors, especially between all members of the youth's medical team, including paediatricians, primary care providers, psychiatrists as well as allied health members. There should also be

appropriate communication and integration of interventions in the education field, where psychoeducation about substance use and related risks should be implemented as part of the emphasis on preventative health care (249). Anybody who claims youth mental health as an important field and has an interest in securing a healthy future for kids can prove their intention here.

4.4.2. International Context

In addition to the consensus process, the Delphi study was able to provide insight into the international overdose situation, current concerning substance use trends, and OAT coverage in 10 different countries, using responses to the semi-structured questionnaire.

As reported in the literature, various countries are not equally affected by the overdose crisis, and overdose fatalities are not evenly distributed across the world. From a recent publication, it appears as though countries can be separated into distinct clusters, with the United States and Canada leading all countries with high levels of overdose (37). These trends seem to be consistent with the feedback that was collected in this Delphi study, and reflected in young populations as well. In effect, panelists from North America reported the most significant harms related to the opioid overdose crisis among youth when compared to panelists from other regions. In Europe and Oceania, panelists reported a relative absence of an opioid overdose crisis, which is consistent with the literature (37,152,260).

These levels of overdose reflect shifts in the drug market and the state of youth treatment systems (37). In effect, the external threat of contaminated street drugs, with fentanyl in particular, is especially dangerous for youth who do not have an established opioid tolerance and are starting to explore street drugs (37). Moreover, the low treatment coverage of OAT for youth in North America, highlighted by the American and Canadian panelists as well as in the literature, do nothing to stop or slow-down the casualties (37). Highly toxic synthetic substances which are widespread in the drugs markets of North America are less accessible elsewhere, especially in countries like Australia and New Zealand, and are contaminating the European and Oceanic illicit drug markets to a lesser extent (261). Nevertheless, concerning trends reported by the panelists in Europe included adulteration of party drugs such as MDMA and GHB, which are

especially popular among youth. Increasing benzodiazepine use has also been mentioned by Swiss panelists, which is similar to the situation in Scotland where benzodiazepines are main drivers of overdose and where fentanyl is not reported as a problem (262). In the Netherlands, an upsurge in the use of registered opioids, in particular the use of Oxycodone, among youth has been a concerning development (263). Though these countries are facing worrying trends, the prevalence of fatal overdose is much lower compared to North America, in part due to the more functional youth treatment systems. OAT is the normal available treatment option in these countries. Though this is not a comprehensive assessment of mental health treatment structures, it does suggest a more functional treatment system able to better address the needs of youth with high-risk substance use. Nevertheless, despite the fact that an alarming level of overdoses among youth is so far only happening in a few countries, there is no reason to believe others will be spared. In the face of changing drug markets and patterns of use, individuals must be supported by well-functioning healthcare systems built around diversity, quality and availability of appropriate treatment options.

4.4.3. Limitations

Limitations to this study are mostly in regard to the representativeness of international expert participants in the panel and review phases of this projects. We were able to recruit 31 participants with representation mostly from Europe and North America. There was a lack of representation from Asian and African countries which may result in a bias of opinions towards consensus that may favour individualism and autonomy – values more prevalent in the countries represented. With any Delphi study, there is possible bias in the views of experts included and a moderate response rate of approximately 70% across all phases of the study could have resulted in biased outcomes.

4.4.4. Conclusion

Internationally, youth mental health care, and especially support for youth with high-risk substance use, is substandard. Due to a critical lack of research, necessary evidence and treatment guidelines are not available. Improvements in treatment through consensus building should lead to necessary next steps of informing health care decision makers and professional

organizations. The work is just beginning. Without change, rising fatalities, especially through overdose, are unavoidable.

This consensus statement combined all prior sections of the thesis by utilizing evidence-based treatment approaches and pre-existing clinical practice guidelines to create recommendations meant to encourage high-quality patient care, based on the international collective opinions of experts.

5. Discussion, recommendations, conclusions

5.1. Summary of study findings

Mental and substance use disorders are the leading cause of disability in children and youth worldwide, which represents a serious international challenge. (28,29). Moving forward, healthcare systems will need to devote more resources to children and youth with mental and substance use disorders to build, revamp, and update treatment systems for youth, as the current systems are outdated and ineffective. This is especially true in the context of the opioid overdose crisis and the COVID-19 pandemic (33–35). This thesis, written at the intersection of two public health emergencies, aimed to contribute to a paradigm shift in the treatment of mental health and substance use disorder among youth, addressing the gap within the field of addiction psychiatry and adolescent medicine. This thesis consists of 3 sections: a narrative review of current treatment approaches, a rapid review of clinical practice guidelines, and a Delphi study for the development of an international consensus statement.

5.1.1. Current treatment approaches

The first section of this thesis was a narrative review that set the stage for the following chapters, as it provided an overview of the current reality of treatment approaches for high-risk substance use among youth, specifically high-risk opioid use. The hypotheses were that 1) there is little-tono clinical research on treatment needs and effective interventions among youth with high-risk opioid use, and 2) medications for OUD are beneficial for youth despite not being readily offered in pediatric primary care. For this narrative review, over 1400 references were identified from the published academic literature using the PudMed database. After full text screening, the narrative review included a total of six review papers, four randomized controlled trials, and nine observational clinical studies. Findings demonstrated that little research has been done to evaluate the effect of OAT in youth, although this treatment option is used among adult globally. From the 19 studies included in this review, medications for OUD seem to be beneficial for youth, suggesting that pathways to OAT should be more readily offered in pediatric primary care. The scarcity of the literature and the difficulty in finding relevant articles were reflected in this narrative review, as well as highlighted in others. Despite the growing needs in this age group, the lack of quality care and treatment coverage is even worse than the situation observed within adult treatment systems. Such a dysfunctional treatment system is certainly due to a

multitude of factors, including the political and ideological biases centered around abstinence and substance use among youth. An evaluation of clinical practice guidelines would allow for further investigation and assess the gap between research and policy recommendations.

5.1.2. Clinical practice guidelines

The second section of this thesis was a rapid review of clinical practice guidelines on the treatment and management of high-risk opioid use among youth, intended to evaluate the legal and political reality of treatment, as well as assess the gap between the practice recommendations and the current evidence. The hypotheses were that 1) there is an overall lack of guidance, structural ideas and treatment concepts surrounding high-risk opioid use and OUD among youth, and 2) the treatment guidelines that do exist for high-risk opioid use and opioid use disorder among youth are either outdated or not being implemented appropriately. This review included searches of the peer-reviewed literature and the grey literature to identify relevant clinical guidelines, defined as systematically developed recommendations produced to direct the management of young patients with high-risk opioid use. From this search, 862 peer-reviewed articles were screened, as well as the grey literature from 34 countries. Only three countries had specific guidelines dedicated to the treatment of opioid dependence among youth. Such shortcomings in the international body of literature surrounding the clinical guidance for the treatment of OUD in youth reflect the inattention to this field within political agendas and healthcare systems. Though the existing guidelines in Canada and the United States do encourage the full range of evidence-based options including pharmacotherapy, only a small proportion of youth receive medication for OUD. The hesitance in using pharmacotherapies for youth among many clinicians as well as parents/caregivers is rooted in an outdated model of addiction and in the idealistic perception that substance dependence is just a phase in development that can be treated through abstinence-based approaches. In order to address necessary reform, system development and international standards, evidence-based international consensus statements were developed to improve the quality of care and achieve better health outcomes among youth with high-risk substance use.

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5.1.3. International Consensus

The third and final section of this thesis was an international consensus on the prevention, treatment, and management of high-risk substance use, based on the combination of scientific evidence and clinical experience, achieved through a modified Delphi process. The hypotheses were that 1) all evidence-based intervention strategies are important to explore with young patients, including pharmacotherapy, and should be used according to the needs and preferences of the patients for maximal engagement, 2) mental health and substance use services must address the specific preventative and therapeutic needs of vulnerable youth by being developmentally appropriate, substance-specific, severity-specific, and risk-specific, and 3) treatment settings and professional teams must receive education and training for proper management of high-risk substance use among youth. A semi-structure questionnaire comprised of five domains (clinical risks, target populations, intervention goals, intervention strategies, settings and expertise) was shared with a panel of 31 experts, and their responses were used to create initial statements. These statements were subsequently revised and finalized through three rounds of rating and feedback. Among the five major domains, consensus was reached for 60 statements, which identified common ground regarding first-line treatment options, including the use of pharmacotherapy as first-line treatment for high-risk substance use in youth, especially opioids and benzodiazepines. Moreover, this work provided a basis for education by outlining important target populations, defining intervention goals, and identifying appropriate treatment settings and expertise, that can be used as support to inform the next level of service development. Immediate research priorities were also highlighted by this work, including involuntary admission and online tools for risk assessment and monitoring. This consensus statement therefore defines a strong framework to address the fragmented and outdated current state of research and evidence-based clinical care. It describes necessary areas of action in all critical domains to improve the necessary response to the increasing overdose cases among adolescents and high-risk behaviors using psychotropic substances.

5.2. Limitations and recommendations for future research

General limitations of this thesis along with recommendations for future research are described below. Specific limitations of the narrative review, rapid review, and Delphi process have been described in the previous sections (Chapter 2, 3, and 4 respectively).

5.2.1. Youth Engagement

In order to provide high-quality mental health and substance use care to children and youth within robust and effective healthcare systems, their perspectives must be sought and their voices heard. Therefore, an important limitation of this thesis is the lack of involvement of youth. Moving forward, very little progress will be made if the management of youth's mental health and substance use is done without connecting with them. Systems currently try to fit youth into services that already exist, but the existing services are not appropriate and do not adequately serve most youth with high-risk substance use. Engaging youth is the first critical step in making services that are attractive and exciting to youth, thereby increasing their engagement with, and retention in, such services (222). For instance, previous studies that have sought to elicit perspectives of street-involved young people regarding their experiences with achieving periods of injection cessation have reported inadequate social supports and abstinence-focused treatment methods as impediments to reduce or stop injecting (264). Conversely, street-involved young people reported refraining from injection drug use when having appropriate access to harm reduction-informed youth-focused services and provision of housing and social supports (264). Adopting mixed-method approaches, such as the ethno-epidemiological methodology, allow for more nuanced and participant-centered research, thereby allowing young people to re-engineer services and re-orient access points that work for them (264,265). Moreover, engaging all relevant stakeholders in the community and combining data from youth, parents, and staff can offer a multifaceted perspective on the substance use treatment experiences, and help determine the elements of substance use treatment that are effective for younger patients and their support network (266). Co-production is a core principle in supporting engagement and ongoing adaptation to suit changing needs (267). Future public health and policy research should consult and integrate youth as knowledge-users (268,269).

5.2.2. Prevention

Preventing the high-risk use or misuse of substances and the development of substance use disorders among adolescents and young adults is a critical component to reducing the burden of disease in this age group. However, much of this thesis has focused on treatment, as opposed to prevention. Future research should continue to examine and develop universal prevention initiatives that aim to deter early-stage high-risk substance use or delay the onset or progression of high-risk use (270). Adolescence is the peak period during which substance use first occurs, with the median age of onset for alcohol and tobacco use being 16-19 years, the onset for cannabis use being 18-19 years, and the onset for cocaine use being 21-24 years across all countries (271). Given this, prevention programs that are effective at educating individuals and equipping youth with appropriate knowledge and skills can help minimize the need for diagnosis, treatment, and management of SUDs in the future.

Schools are the focus of most attempts to develop and test evidence-based prevention approaches, mainly because they offer access to large number of adolescents and allow youth to participate and engage in these services with minimal disruptions (272). Literature reviews and meta-analytic studies have shown that school-based prevention programs can reduce various forms of substance use in young people, and outcome studies have demonstrated clear evidence of short and long-term effects on substance use behavior (273–279). Programs that are highly interactive, skills-focused, and implemented over multiple years tend to be the most effective (274,280). Climate Schools represent a good example of a student- and teacher-led, curriculumbased, program aimed at preventing harms related to substance use, and which has been shown to delay initiation of substance use, reduce substance use and mental health symptoms, and increase substance use and mental health knowledge (246–248,281).

Along with school-based prevention programs, a variety of family and community level prevention programs have also been effective for youth substance use and have strong evidence to support their use (274,282–284). In particular, family-based prevention programs that focus on parent-youth dyads by combining parenting skills and family bonding components, as well as community-based prevention programs that focus on making the community a more protective environment by presenting a coordinated, comprehensive message across multiple delivery components, have been found to be most effective in changing behavior among youth (274,282,284–288). Nevertheless, future efforts must widely disseminate effective prevention programs that are supportive of youth from different cultural backgrounds and that address the common and different needs of groups of youth (273,274,280,289).

5.2.3. Early Intervention

The window for targeted intervention to prevent progression from incidence of substance use to regular substance use and development of SUD is critically small in adolescents. In fact, a substantial proportion of transitions from onset to higher frequency of use and problematic use typically occur within the 3 years (290). Moreover, certain factors contribute to a higher vulnerability for shorter transition periods, including family history of mental health and substance use disorders. Though the importance of early intervention in youth has been acknowledged throughout this thesis, especially in the consensus statement, more work needs to determine the most effective intensity and duration of interventions, expand early intervention beyond psychosis towards the full diagnostic spectrum, and widely implement targeted early interventions programs (291–293).

Tools such as electronic mental health (EMH) interventions have been brought forward as solutions that can bridge the many gaps in early intervention coverage for all major mental health and substance use macrophenotypes (28,294–296). This online reform towards web-based platforms can cover not only early intervention, but also be extended to the entire care continuum including prevention, brief screening, treatment, and management. Technology-based interventions can be more accessible and cost-effective than traditional face-to-face treatments, while also more effective than standalone treatment when used in conjunction with medication-assisted (297). Successful EMH platforms for youth mental health services have been produced by different governing bodies including Headspace and Orygen in Australia, Jigsaw in Ireland, and Youthspace in England (265,295,298–300). Web-based interventions are therefore highly suitable for delivering a continuum of care, starting from early diagnosis and intervention to continued peer/professional support, and represent a major solution to improving the coordination between services that address a range of needs among youth (301,302).

5.2.4. Overdose events

Very little is known about the young individuals who are dying from opioid overdoses or suffering from severe adverse outcomes (303). Studies have reported opioid use (e.g., prescription opioids, heroin, mixing), tranquilizer use (e.g., barbiturates, benzodiazepines), and

injection drug use as important risk factors for drug overdose in young people (304). Moreover, polysubstance use, psychiatric comorbidity, witnessing an overdose, and being unstably housed were other reported risk factors (304). Though the aforementioned risk factors are also common to adults, youth have additional risks that are unique to adolescence and young adulthood: inexperience and underestimation of the drug effects among youth, social environments that facilitate 'binge' substance use, lack of 'safe' drug use skills, developmental overconfidence in one's ability to manage risky situations, conflict at home with parents or caregivers, etc. Collecting statistics on severe adverse events such as overdoses and hospitalizations is not sufficient; collecting treatment data and specific outcome indicators is much more effective. A systematic overview of the young substance using population is necessary to inform and control the quality of care, costs and outcomes of the system (305). A dearth of information regarding the relationship between SUD treatment history and drug OD in young people is apparent. More studies are needed to appropriately design addiction treatment and prevention efforts aimed at reducing the risk of overdose in youth.

5.2.5. Treatment options for OUD

Conclusions drawn from experts in the field as well as from thorough reviews of the literature have demonstrated overwhelmingly that there is an urgent need for more clinical research focusing on improving models of care for high-risk substance use in adolescents and young adults (179). Youth-specific randomized controlled trials and high-quality observational studies that assess the potential risks and benefits of different treatment modalities must become a priority in psychiatric research. As a general rule, any high-quality study that is being done among adults should also include a small subsample of youth. Moreover, the published literature on OAT and other medication-assisted treatment approaches contains a wealth of "hidden" data on young adults between ages 18 and 25 years. Due to dearth of clinical research on the effectiveness, safety and tolerability of OAT in patients aged 18 to 25 years, studies should think of extracting and evaluating data on this patient population from completed clinical trials and observational studies. The position paper from *The Society for Adolescent Health and Medicine* offers several research questions that are worth exploring immediately (178). For instance, the efficacy, effectiveness, optimal duration, and cost-effectiveness of medications and medication delivery models. Moreover, retention in the first year of substitution treatment is low in Canada

(around 35.1% in British Columbia for OAT in 2016) (306). The quality of care provided to youth is evidently not sufficient nor satisfactory if the majority of clients are lost at follow-up. Future research must aim to determine the treatment strategies that will maximize the retention and survival of youth with high-risk opioid use, which begins by prioritizing clinical research and making youth feel welcomed rather than dismissed (267).

5.3. Implications and considerations for policy and practice

The work presented in this thesis has several policy and practice implications. Namely, the need for a paradigm shift towards evidence-based interventions and youth-specific services.

5.3.1. Paradigm Shift

Opioid-related overdose mortality has continuously increased over the last 20 years among adults and youth alike. However, unlike adults, youth with OUD have not benefitted from the progress that was made in clinical practice and public health policy. For example, buprenorphine and methadone have been associated with reduced overdose and opioid-related morbidity when compared to other treatment pathways. Yet, less than 2% of youth receive pharmacological treatment within 30 days of experiencing an overdose (84,307). The continual increase in the global prevalence of SUDs among youth, despite success of diverse intervention measures, can be regarded as a complete health policy failure. A massive overhaul is urgently needed in Adolescent Psychiatry, as well as healthcare systems more generally, in order to adequately respond to the mental health and substance use needs of children, adolescents, and young adults from around the world. The abstinence paradigm and ideological biases have too narrow of a focus, centered around an avoidance or prohibition of use, which leaves youth ill-equipped at identifying and mitigating harms related to substance use if/when they consume. A therapeutic continuity that bridges abstinence-based and harm reduction treatment communities must be made available to youth. Interventions that fall under the harm reduction umbrella, such as those that prevent youth from dying or experiencing serious adverse outcomes as a result of substance use ("staying alive"), those that protect youth from harms related to their substance use such as blood-borne viruses ("maintaining health"), and those that help individuals control and reduce their use ("getting better"), must be made contextually relevant and responsive to the lived experiences of youth (222,308). Without a shift towards harm reduction measures and evidencebased interventions in the context of a consistent healthcare system response, the burden of mental health and substance use disorders will likely continue to escalate among youth in the coming years. Instead of an abstinence-only model, youth should be guided and supported in their decision-making, towards an approach of their choosing that is along the therapeutic continuum.

5.3.2. Evidence-based practice in adolescent psychiatry

Reaching consensus on overall effectiveness of interventions can take decades to develop. However, evidence-based practices for high-risk substance use among youth have been clearly outlined in this thesis, based on up-to-date research and international clinical experience. Pharmacological evidence-based treatments, such as OAT for opioid dependence, are far more effective treatment options than abstinence-based treatment, and physicians in primary care recommend substitution treatment over abstinence-based treatment for all patient groups, including adolescents (146). Healthcare systems, especially in North America, must expand access to pharmacological interventions by minimizing the barriers to the receipt of medication for youth, educating all healthcare professionals who work with adolescents and young adults, and implementing strategies that reduce the stigma surrounding the use of medication for substance dependence among youth (178). The relative lower effectiveness of OAT among youth, compared to adults, is likely due to the lack of youth-specific modalities and the incompatibility of youth in adult treatment programs. The amalgamation of evidence-based medications for opioid dependence must be offered to youth, and exceptions to using specific mediations for OUD in youth need to be justified through clinical research that prove that the positive effects shown for adults are not to be expected among adolescents. Moreover, psychosocial intervention strategies such as family therapy, motivational interviewing, cognitive behavioral therapy, and peer support have also been established as important evidence-based approaches for youth (309–312). It is critical not only to address withdrawal symptoms but also to address the multiple challenges patients are coming in with, including unbelievable burden of early and/or ongoing trauma, suicidal ideation, severe concurrent disorders, etc. Instead of resorting to idealistic measures and politically driven agendas (e.g., abstinence), providing coordinated addiction treatment services across a continuum of care would better combat the risk of severe harm and death related to substance use among youth (251).

5.3.3. Development of youth-friendly services

The development of low-threshold, youth-friendly, and stigma-free services that are interesting and safe for youth are essential. Youth in adult treatment facilities often indicate feeling intimidated by and unwelcome in adult addiction services. There is a need to devise ways to overcome structural barriers to improve service coordination for youth at the organizational and system levels (267). Youth with markers of vulnerability, such as severe housing instability, high-intensity drug use, recent interactions with law enforcement, drug dealing, violence, and histories of physical abuse, are more prone to have difficulty accessing service (313). This highlights the need for structural level initiatives that can improve service access and healthrelated outcomes. Youth have reported the importance of flexible transition timing and individualized transition plans as positive factors during transition between youth mental health services and adult mental health services (314). Public health and policy initiatives that remove of age restrictions for services, introduce a continuum of services with gradual age transitions, establish youth-centric social housing and support adolescent-responsive health systems are essential to lowering the structural barriers and improving the accessibility of care and services for vulnerable youth (313). More studies that document the trajectories of youth receiving child and adolescent mental health services as they cross the transition boundary are urgently needed (315).

5.4. Conclusion

The main objective of this thesis was to contribute to a paradigm shift in the treatment of mental health and SUDs among youth and to address the gap within the field of addiction psychiatry and adolescent medicine. The dysfunctional treatment system and lack of academic efforts in this domain are devastating. A need for more clinical research on effective interventions among youth with high-risk opioid use is evident. Medications for OUD such as buprenorphine and methadone seem to be beneficial for youth, but more youth-inclusive or youth-specific high-quality studies must be performed to decisively determine the safety and clinical effectiveness of various treatment options among younger demographics, and to appropriately develop interventions that are compatible with youth. However, medicine is not only driven by evidence but also by political bias like prohibition and abstinence. The quasi-absence of clinical guidance,

structural ideas and treatment concepts relating to high-risk substance use in youth internationally reflect the inattention to this field within political agendas and healthcare systems. Though the Canadian and American guidelines recommend the use of medication for OUD among youth, a bias towards abstinence still seems to dominate the clinical field, thereby creating barriers to the receipt of medication for OUD. To educate treatment systems, prioritize prevention and early intervention, and promote access to appropriate treatment resources, the medical communities must collectively respond to the mental health and substance use needs of youth. An international consensus statement represents a first big step in the creation of baseline recommendations which can be used to promote interventions of proven benefit and discourage ineffective ones, in an attempt to improve quality of life as well as reduce morbidity and mortality among youth with high-risk substance use. The healthcare system as a whole must be better trained in dealing with SUD among youth, especially given the prevalence of substance initiation in that age group. It is our duty to provide youth with the appropriate resources that enable substance-using youth in living a self-determined life without impairment through substance use. Online tools for risk assessment and monitoring represent promising avenues from a public health perspective. More critical however is the need to dramatically improve quality of treatment and treatment coverage for high-risk substance use in youth, which starts with a paradigm shift within the field of addiction psychiatry and adolescent medicine, as well as within healthcare systems more globally. So long as the care for mental health and substance use disorder among youth continues to be substandard and negligent, their fundamental human rights of access to the highest attainable standards of health continue to be violated.

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Appendices

Appendix A: Delphi Study Semi-Structured Survey

A. Outlining clinical risks/concurrent conditions

1) What are the primary substances for which youth enter treatment in your city, country?

2) What substances are associated with the most severe adverse consequences in your country?

3)How has the overdose crisis effected youth in your country?

4) Do you think that the clinical assessment and the focus for substance use should include adolescents (12-17 years) and young adults or transitioning youth (18-25)? Should they be addressed and evaluated in a common target age frame?

5) What is your experience with high-risk substance use among youth and give examples of the most concerning developments in your country?

6) Which assessment domains and psychometric tools are critical for the understanding and monitoring of high-risk substance use among youth, defining high-risk as the likelihood of serious adverse events (overdose, self-harm, binge drinking)?

In prevention: In treatment:

7) Which domains and psychometric tools can be used for "online risk assessment and monitoring"? Are you aware of existing developments or solutions?

In prevention: In treatment:

8) Should the assessment of user's engagement and satisfaction be part of routine assessment and when should it happen?

9) How should the substance use best be documented and monitored? Are there youth specific categories or items?

10) Below are critical domains beyond immediate substance use. How should they be included and addressed? Please also suggest additional critical domains that are not listed.

- Family
- Social/relational/interpersonal
- Early trauma
- Mental health risks
- Cognitive capacity and academic/vocational achievement
- High-risk behaviors (unprotected sexual activity, drinking and driving), etc.
- Others:

11) Below are severe adverse events related to risky substance use. How should they be addressed? Please suggest additional severe adverse events and how they should be addressed.

- Overdose
- Binge drinking
- Injection
- Emergency room visits
- Suicidal ideations and attempts
- Crisis/acute clinical admission
- Psychosis
- Others:

B. Determining target populations

1) Given their unique issues, adolescents with substance use disorder benefit from services designed specifically for them. Among youth, there are different age categories, levels of substance use and risk-taking, reasons for substance use, and preventative and therapeutic needs. How would identifying specific subpopulations aid in the prevention and treatment of adolescents with SUD?

2) Consider and comment the following cluster:

- Adolescents whose parents suffer from substance abuse
- Adolescents with exploratory use
- Adolescents with high-risk exploratory use of non-opiates (binge drinking, intoxication in public, chain smoking, stimulants etc.) and or living in a marginalized environment (foster care, homelessness, forensic etc.)
- Adolescents with severe concurrent conditions (suicide attempts, violence, severe trauma, psychosis)
- Adolescents with exploratory opioid use or regular crack-cocaine use
- Adolescents injecting opioids or other psychotropic substances

Are there any specific target populations that have not been mentioned?

C. Defining intervention goals

1) What should be the main goals of treatment for youth with SUD which should always be included in the treatment planning?

2) When should harm reduction be an appropriate treatment goal for youth?

3) How should harm reduction services be organized? Should they always be youth specific? Please give examples.

4) How should overdose prevention be integrated into the system?

5) In your perspective, what are the 3 main risk factors for overdose among youth?

6) How should youth be taught about their risks and how to manage them?

7) When and how should abstinence vs. controlled use be addressed in the treatment trajectory of youth?

8) Should screening and risk assessment of the general child and adolescent population be routinely integrated into youth mental health care? How about among youth with a family history of SUD or mental health? Should screening happen for all users following a certain age cut-off as an opportunity to assess for use, provide psychoeducation and engage in discussion in future?

9) Should school-based programs be implemented in general? If so, are you aware of any effective evidence-based programs that should be standardized?

10) Do you think online resources should be used to support these strategies? Are you aware of existing models?

D. Recognizing evidence-based intervention strategies

1) Consider the following: youth who do not meet criteria for SUD or have at risk use should be offered age-appropriate advice and/or an extended brief intervention to discourage further use. These interventions should be youth adapted and engaging. How can that be achieved? Consider the following strategies:

- Harm reduction
- Overdose prevention
- Risk management
- Motivational enhancement
- Behavioral management

2) Please rate these interventions on a 5-point scale from the following list in relation to their significance and importance as a core set of treatment for youth, 0 being "not at all important" and 5 being "extremely important".

- Safe injection sites:
- Harm reduction programs:
- Drug testing programs:
- Contingency Management:
- Detoxification and withdrawal management:
- Pharmacologic interventions:
- Long term abstinence-based inpatient rehabilitation:
- Family therapy (e.g., MST, CRA, CRAFT):
- Psychotherapy/Counselling (e.g., CBT, CM, MI, etc.):
- Integrated treatment of comorbid disorders:
- Mental health care:
- Physical health care:
- Psychosocial/peer support:

3) Among the pharmacological interventions primarily aimed at treating SUD, which do you consider to be the first line for youth and why? Consider the following substances being used:

- Nicotine:
- Alcohol:
- Opioids:
- Cannabis:
- Stimulants:
- Others:

Are there useful strategies not following guidelines and if so which?

4) Among adults, opioid agonist treatment (OAT) is commonly done with Methadone, Suboxone (buprenorphine/naloxone), Kadian (slow-release oral morphine), etc. In your experience, are any safer and more effective for youth? Should any of these opioid agonist medications be especially be recommended or emphasized in the treatment for youth?

5) In your country, what is the prevalence of youth with high-risk opioid use/OUD in OAT?

- OAT is the normal available treatment option
- OAT is only used as exception
- OAT is not recommended and not used

Additional description of the coverage of OAT for youth in your country:

6) In your country, are the needs of youth being reached? If not, please outline the 3 most important steps to achieve this.

7) How can the number of youths retained in OAT be improved?

8) When should long term abstinence-based inpatient rehabilitation be considered?

9) Among the psychotherapeutic interventions, which do you consider to be the first line for youth and why?

10) What are the different evidence-based psychotherapeutic interventions that you would recommend using for youth?

11) How do you make treatment approaches/plans for youth developmentally appropriate?

12) Parental/family involvement in the treatment of youth with SUD is complicated. Adolescents may still live at home in which case parental involvement would be relevant. It might be mandatory to involve parents in the treatment of minors in some countries. Regardless, parental involvement should not be barrier to treatment. When is it appropriate for a young person's parent or carer to be involved in the treatment with youth? Conversely, when is it less appropriate/helpful to involve the parents or caregivers?

E. Identifying appropriate treatment settings and expertise

1) What should define the core of treatment and recovery for youth?

2) How could youth be best supported in the following treatment settings:

- 2a) Harm reduction facilities
- 2b) Low-threshold facilities (such shelters, meal services, etc.):
- 2c) Emergency rooms (in case of OD, binge-drinking, etc.):
- 2d) Acute care inpatient:
- 2e) Day clinics:
- 2f) Outpatient:
- 2g) Outreach:
- 2h) Intensive Care Medicine:
- 2i) Long-term rehab:

3) What expertise or specialty should be principal to the treatment and recovery of youth? Consider the following:

- Pediatrics
- Primary care
- Adolescent Psychiatry
- Adult Psychiatry
- Addiction Psychiatry
- Adolescent Medicine
- Other professions (e.g., social workers, etc.)
- Others not mentioned:

4) How should medications be best provided in treating youth with SUD?

5) How should be the relationship between substance use specialists and other primary care professionals in the treatment of youth mental health problems?

Appendix B: Sharing Case Stories

Case Story 1 - Submitted by MMK, Egypt

Patient age: 16 Setting: Outpatient

Substance use history:

- Substance used/amount/frequency: Heroin 1mg daily; Tramadol 225mg daily; Cannabis daily
- Overdose history: one accidental opioid overdose

Diagnosis:

- Polysubstance
- PTSD
- Substance-induced manic episode (which pushed his family to seek treatment)

Treatment history:

- 3 past attempts with symptomatic treatment and stopping cold turkey
- Pharmacotherapy: Symptomatic treatment with benzodiazepines, NSAID, antidepressants, mood stabilizers
- Psychosocial treatment: motivational interviewing, dialectical behavior therapy, cognitive behavioural therapy

Case story 2 - Submitted by MP, the Netherlands

Patient age: 17

Setting: Male, lives at home, parents are not separate, 3 siblings. Peer group also uses drugs.

Substance use history:

- Substance used/amount/frequency: Amphetamine (Speed) daily, as much as he can afford; Cannabis daily 1g; Alcohol on weekends
- Overdose history: one time, ended up at the ER

Diagnosis:

- SUD (Speed and Cannabis abuse)
- MDD
- PTSD
- ADHD
- Family problems

Treatment program:

- Diagnosed with ADHD early in school as well as having a discrepant intelligence profile (substantial difference between individualized test of general intelligence and academic achievement)

- Outpatient care was not sufficient enough, so he was admitted for detoxification, followed by family treatment and emotion regulation after being discharged
- ADHD medication was started but the medication induced a craving for speed, so this was stopped.
- He didn't want EMDR (Eye Movement Desensitization and Reprocessing) just yet.
- He stayed clean for 2 years on his own and worked hard till he had a relapse in cannabis.
- Currently indicated still using cannabis but attending CBT
- ADHD medication started again with better results
- EMDR and schema therapy are also happening
- Individual system therapy started because of a family issue that weighs heavily on him

Case story 3 - Submitted by RA, the United States

Patient age: 25

Setting: I see him in outpatient treatment, also several recent resident treatment admissions, and living in recovery house

Substance use history:

- Substance used/amount/frequency: crack cocaine, heroin, cannabis, alcohol; all daily; unsure of amount
- Overdose history: None

Diagnosis:

- Opioid use disorder
- Alcohol use disorder
- Cocaine use disorder
- MDD

Treatment history:

- Has been in residential treatment over 8 times in last 8 years
- He is on Sublocade for his OUD which works well; has not used heroin in a while, but continues to use crack cocaine daily

Appendix C: Meeting Minutes to the Delphi Webinar

Present: Jean Westenberg, Marc Vogel, Renske Spijkerman, Michael Krausz, Martha Ignaszewski, Vivian Tang, Jeanette Rohrig, Laura Orsolini, Sharon Levy, Dzung Vo, Marc Fishman, Gerhard Rechberger, Hannes Strasser, Julie Elsner, Mostafa Kamel, Nickie Mathew, Jessica Moe, Janet Suen

Goal of meeting: To discuss statements that have not reached consensus (statements with at least two panelists disagreeing).

Object of Study: The objective of the Delphi study is to reach a consensus among panelist on statements relating to the screening, treatment, and management of high-risk substance use in youth and publish these statements.

Discussion #1: Screening

Revised Statement	Routing screening for substance use and related risks by primary care provider using brief clinical assessments is recommended in all youth.
New Statement	Screening for high-risk substance use and substance use disorder in primary care and mental health treatment settings is recommended in all youth if feasible, however priority should be given to screening young people known to be at risk of mental health problems or who have a family history of SUD.

- Would remove "if feasible" from the statement, this gives providers an excuse to not do the screening. It IS feasible to do universal screening
- First statement is good as is, second statement needs to change
- Agrees that "if feasible" should be removed; underscreening means potentially not recognizing someone that is high risk; and by not screening for high-risk substance use we are watering down the assessment process
- All PCPS and MH providers should be screening for substance use
- Agrees that "if feasible" should be removed; if screening is not feasible then the whole primary care system needs to change
- In addition, non-mandatory screening may mean the provider is making other assumptions about the youth's risk (i.e, racism)
- Should add something about confidentiality into the statement (screening needs to be between only the youth and provider, not parents)
- We do not need both statements, second can be left out; adding the confidential portion to the first statement is sufficient
- Need to include the words "mental health screening"; agrees with adding confidentiality

Revised	The primary goal in treating youth with SUD is to improve functional outcomes
Statement	and support substance-using youth in living lives without impairment through
	substance use.
Revised	SUD treatment should be evidence-based and goal focused. It should be
Statement	provided in partnership with youth and their providers and incorporate a range of

Discussion #2: Primary goal in treatment

modalities including reduction in use, reduction in harm, pharmacotherapy,
healthy coping with mental and physical distress, treatment of co-occurring
disorders, etc. Goals should aim to optimize function and promote safety via a
recovery framework and be incremental, specific, measurable and achievable.

- Do not need both statements; second is better but needs to be modified
- The second statement should include the words "reduction in overdose death" in addition to harm and safety; needs to be blunter
- Could add "reduce mortality" and "promoting resilience and positive youth development" to second statement
- Second statement is better; should add something about protecting health and lives, not just improving function
- Take out the "etc" in examples leaves too many possibilities; all statements should be conclusive
- Do we need to detail all the types of treatments offered? If we removed the list of interventions the statement will be more concise
- Would recommend only using the second statement but making it crisper
- The goal of helping youth live life without impairment and increase function is a good statement because it does not condemn; likes the non-impairment part of about it. Would like to see it in the second statement
- Agrees with the "improve function" language, should we write that the goal is NOT abstinence (should we add the word in somewhere?) these goals are individual goals maybe the goals can help to say that the goal for each youth is different
- Need to be focused that the goal is about substance use. There is no mention of addressing substance; need to make it clear it is Hight Risk SU ("Substance related impairment")
- Likes "without impairment" in the first statement

Discussion #3: Involuntary admission

Revised	Involuntary treatment should be considered for the extremely small percentage
Statement	of youth who have an acute risk of significant impairment (or death) and for
	whom all other treatments options have failed. Involuntary treatment should be
	nested within a broader comprehensive care plan and used for as brief a period
	as required.

- BC Children's is piloting stabilization care including involuntary admissions, NOT involuntarily treatment; need to separate admission and treatment in the statement
- There is a difference between stabilization care (a few days to interrupt a cycle) rather than treatment (e.g we will admit a patient involuntarily but not give OAT voluntarily)
- Point is to break the cycle (people presenting to ODs ever week) not talking about most kids or people using, but people who are not accessing harm-reduction, not accessing voluntary services even when they are offered and tried
- May want to think about youth's capacity (what is the capacity of a youth when they are 13th with FASD who just overdoses, has seizers, hypoxic what is their capacity to make a decision and parents are begging the hospital to keep the kid?)

- Would change statement to involuntarily admission not treatment; add something about short-term admission
- Add information about involuntarily care if there is imminent harm
- The approach is very different between adult and children; inserting something about reinforcing this as a last resort? They statement does not convey this with enough clarity
- Add something about needing a shared decision with youth and family; to ensure that all avenues are exhausted before this is stated
- Worried about this statement; we are in international audience and when we put the weight into a statement, it gives the air that it is a proven technique
- Worried about unintended consequences, if youth know they can be held against their will if they seek treatment, they are less likely to see treatment; the pilot project is a good idea but a statement of this weight and certainty is dangerous when we do not know what the outcomes are overall
- Complex because different countries have variation of treatment options- this needs to be recognized ("IF this is an option this has to be placed into context")
- Do not like the working of "treatment when other treatments have failed" this is not the time when we use involuntary commitment. This sounds like the patient is continuing to struggle SO we go involuntarily; there is a time and place, it is very narrow, it is for stabilization and should be used when someone is at risk of life; in US it is mostly with adults and for younger kids there are other mechanisms
- It depends on the legal structure of the country; in the Netherlands if they are harmful to themselves it is a legal order that it is a clinical admission for 2 days and this can be done with young people and adults
- Attention to a due process and protection of legal rights need to be built into the statement
- Statement should emphasize engagement in treatment (we want youth and families to be engaged
- Add a component of including the need for a more systematic evaluation of all these measures and thorough clinical research
- Agree with change of "treatment" to "admission"
- Would change "required" to "possible"
- Would include the need for systematic research

Discussion #4: First-line treatments

Consensus	For nicotine dependence, evidence-based medication treatments including
Statement	nicotine replacement treatment (NRT) and e-cigarettes are recommended as the
	first-line intervention and should be combined with psychosocial interventions
	if possible.
Consensus	For opioid dependence, evidence-based medication treatments including
Statement	buprenorphine, naltrexone, and methadone are recommended as first-line
	intervention and should be combined with psychosocial interventions if
	possible.
Revised	For stimulant dependence, behavioral interventions such as contingency
Statement	management, motivational interviewing, cognitive behavioral therapy, and

	family therapy are recommended. Medication may be required to manage
	problematic symptoms, particularly in stimulant withdrawal.
Revised	For benzodiazepine dependence, it is recommended that pharmacotherapy
Statement	involving the gradual tapering of long-acting benzodiazepine agonists be
	considered as first choice treatment, despite the lack of evidence. Behavioral
	interventions such as contingency management, cognitive behavioral therapy,
	and family therapy are also recommended along with symptomatic treatment.

- Agreement with statement one after adding "If kids want to be abstinent of nicotine consumption" and after removing mention of e-cigarettes
- If e-cigarettes are left in the statement, would retract the whole statement; e-cigarettes are very controversial in Holland
- E-cigarettes are not recommended for youth
- For statements on benzo tapering needs to emphasize that this needs to be done very slowly
- Statement on Benzos is confusing; what if someone presents with Benzo withdrawal we will try to taper, if they are not in withdrawal, they will do behavioral treatments instead (
- Language of long-acting Benzo agonist confusing what are we talking about? We can remove that
- There is no such thing as a Benzo agonist; remove this
- Should add something about "to be considered as evidence emerges"
- Would not include naltrexone as first-line medication

Discussion #5: Family involvement

Consensus	It is recommended to have the parents or caretakers involved in treatment as
Statement	much as possible. However, limited or no parental involvement should never be
	a barrier to treatment for youth.
Consensus	If the parents/caretakers don't support treatment initially (often due to a
Statement	misunderstanding or preconceived notion) their involvement should continue to
	be encouraged via education, enhancing trust, relieving concerns etc. as better
	family support usually improves outcomes.
Revised	Family involvement can be counterproductive in certain situations such as
Statement	significant family conflict, abusive relationships and estrangement. Youth have
	a right to direct who is involved in their treatment and this should be respected,
	as overriding the young person's autonomy may lead to disengagement from,
	and mistrust of services.

- There needs to be mention of child protection in situations of abuse and risk of violence; if we are aware of a harm to a child, we can qualify this as extreme situations where confidentiality cannot be kept
- Need to add the possibility of breaking confidentiality if youth are at risk of death
- Problem is that numbers show that the kids later on as high-risk drug users report early childhood trauma; so it is not an exception, it is the rule

• We need to be aware; add "interventional strategies are to not work with family as the whole but to work with the guardians the kids in parallel yet separately until they agree to have common sessions