RUTH OVERVIEW

The Research on the Utilization of Therapeutic Hydromorphone (RUTH) study examined 131 individuals between 2016 to 2018 receiving two forms of injectable opioid agonist treatment (iOAT) – diacetylmorphine (pharmaceutical grade heroin) – and hydromorphone, for the treatment of opioid use disorder (OUD). IOAT is a state-of-the-art OUD treatment option for a number of individuals for whom traditional treatment approaches have not worked. The aim of the RUTH study was to determine the effectiveness of iOAT for individuals transitioning to this treatment after receiving iOAT as part of a blinded randomized clinical trial where they did not know what form of iOAT they were receiving. Participants received open-label medication in RUTH, meaning the medication received was not concealed from the participant or researchers, at Crosstown Clinic in Vancouver, BC, where it was dispensed and self-administered under the observation of a nurse. Those enrolled in the study also completed comprehensive self-reported questionnaire packages at eight timepoints over 18 months and a select number completed one-on-one interviews.

1) Effectiveness and open-label hydromorphone

The former SALOME study site (Crosstown Clinic in Vancouver) was the first to offer open-label hydromorphone. The RUTH study demonstrated that open-label injectable hydromorphone can achieve the same effectiveness as it demonstrated within the double-blind SALOME trial. Retention (i.e. remaining in treatment) among those receiving open-label hydromorphone in RUTH was 77.8%.

Implications

These findings are a crucial component of evidence-based expansion of iOAT clinics – particularly where and if diacetylmorphine is not available. These findings suggest that hydromorphone programs, using similar protocols to the Crosstown Clinic, will be able to reach and engage individuals with severe OUD.

Actual and potential Impacts

Participant retention among those receiving open-label hydromorphone, and not diacetylmorphine, has significant relevance in contexts where diacetylmorphine may not be commercially licensed or politically palatable.

2) Safety during induction period of iOAT

Our team was the first to publish clinical induction protocols for injectable diacetylmorphine and hydromorphone and to investigate its safety in the context of iOAT for opioid use disorder. With data from 3 Canadian studies, encompassing a total of 2993 induction injections, we demonstrated that a 3-day induction protocol allowed patients to safely reach high doses of injectable hydromorphone and diacetylmorphine in a timely manner. There were 34 related somnolence and adverse event (AE) overdoses (4.899 per 100 injection days) in diacetylmorphine and 6 (1.467 per 100 days) in hydromorphone. Four opioid overdoses requiring naloxone (0.571 per 100 injection days) were registered in diacetylmorphine and 1 in hydromorphone (0.211 per 100 injection days), were all safely mitigated onsite.

Implications
Our work offered, for the first time, the opportunity to explore and discuss an induction protocol with injectable diacetylmorphine and hydromorphone in the context of iOAT for opioid use disorder. A fast induction protocol allows clients and providers to engage in treatment safely in a timely manner. This was the first study to investigate the safety of an induction protocol for injectable diacetylmorphine and hydromorphone for iOAT in the context of opioid use disorder and confirmed the safety of iOAT during both induction and after.

Actual and potential impacts
Induction protocols and findings from RUTH have been integrated into provincial and national iOAT clinical care guidelines and have been used across Canada.

3) Dose and Dose adequacy
Our research was the first to examine typical doses of iOAT received and provided in real-world settings and to demonstrate that clients have a preference of medication and are able to moderate their dose accordingly. Participants on iOAT were found to use the entire range of possible iOAT doses (106 –989 mg per day for diacetylmorphine and 51.1 –696.1 mg per day for hydromorphone), however most use the mid-range doses with a subset stable at high and low doses. Participants receiving injectable diacetylmorphine throughout the double-blind and subsequent open-label study period reduced their daily dose of diacetylmorphine (-78.3mg) once they knew which medication they were receiving. Indicators of dose satisfaction revealed communication, in particular client's perspective of the doctor involving them in decisions as much as they want as the strongest indicator of dose satisfaction – not whether the iOAT dose was higher or lower. Potency ratios for diacetylmorphine and hydromorphone were also found to be in the range of 1.4:1 and 1.6:1 which slightly lower than previous clinical trials (2:1).

Implications
IOAT dose ranges are wide and service users utilize the entire range. Evidence supporting typical doses of iOAT can be integrated into program planning to better allow providers and prescribers to engage in individualized care and shared decision-making with service users. Participants lowering their injectable diacetylmorphine dose once they know they are receiving the medication they want reflects the complexity that surrounds client-prescriber relationships and exemplifies how the provision of medication alone is not responsible for an individual's treatment trajectory. This finding has impact for person-center care in OUD.

Actual and potential Impacts
To our knowledge, no other research that has examined the range of typical iOAT doses received and provided in real-world settings. Other iOAT setting can benefit of this studies during program planning.

4) Clients' experience in iOAT
Our team has pioneered the systematic development and use of tools and methods exploring clients' perceptions in the context iOAT. As injectable treatment is a very politicized treatment it is provided in highly regulated environments. Thus, traditionally the focus of studies has been to prove safety and efficacy, with little space to explore how clients feel about the care they receive. Using the Client Satisfaction Questionnaire (CSQ-8), our team went beyond the satisfaction

scores, that are usually high in health care, and collected open-ended positive and negative comments which generated a rich study of the preferences, needs, and attributes of iOAT that were important to participants over time. We were the first to apply a multi-methods and longitudinal approach to examining participants' perceptions and satisfaction with iOAT. We have also conducted in-depth qualitative interviews, exploring participants experiences of person-centered care in iOAT and how relationships with healthcare providers can be constructed in a way that they experiencing care responsive to their needs. Also, for the first time in iOAT, we looked into participants' ratings of physician communication, which revealed physician communication ratings to be lower than those in other populations including emergency departments and trauma centers.

Implications
These findings have substantial and timely research and clinical implications given increasing interest in person-centered practices. Likewise, they are being used to support the development of patient-reported outcome measures (PROMs) within iOAT. There is an increasing need for the expansion of person-centered care within OUD and our findings add to this growing body of literature demonstrating its importance within iOAT.

Actual and potential Impacts
These findings are the first to purposively examine aspects of person-centered care within oral and injectable opioid agonist treatments, highlighting concrete areas for future PROMs development within iOAT. If developed, PROMs within iOAT could be used to inform and guide patient-centered care and clinical decision making. The collection of ratings of physician communication skills can prepare physicians to advocate and connect their patients to services aligned with their needs.

5) Dextroamphetamines
As it happened with the induction protocols, Crosstown Clinic, our long-standing clinical partner, was the first to implement protocols to prescribe stimulants for stimulant use disorder. Our team demonstrated the safety and feasibility of how dextroamphetamines could be used in the context of iOAT. Participants acknowledged that engagement with iOAT helped them to better manage their stimulant use, and offering them dextroamphetamine was well received, although it was not the best alternative for everyone. Perceptions of the effectiveness of dextroamphetamines for stimulant use disorder are also often influenced by the extent to which this medication could provide a substitute for the effects offered by illicit stimulant use; the reaching of a preferred dose; and the ease of medication access. The substitution effect often served as a pre-condition for supporting reduced illicit stimulant use, or abstinence in cases where this was the participant's goal.

Implications
For clients with opioid use disorder and concurrent stimulant use disorder, access to iOAT can promote the self-management of illicit stimulant use. Differences among participant stimulant use profiles provides further justification for considering diverse approaches to the delivery of dextroamphetamine in order to best respond to patients' preference.

Actual and potential Impacts

In Canada dextroamphetamine is licensed for the treatment of ADHD and narcolepsy and can be prescribed off-label for stimulant use disorder. In the absence of available alternative medications, the potential benefit of dextroamphetamine remains among people who continue to use illicit stimulants to achieve euphoric effects. Several settings across BC have been using Crosstown protocols and the published evidence from this study to support their efforts on expand the use of dextroamphetamine if clinically indicated.