Irish Journal of Psychological Medicine, (2023), **40**, 535–537.

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Irish Journal of Psychological Medicine, **40** (2023).
doi:10.1017/ipm.2021.62

An overview of recent advances in opioid agonist treatment (OAT)

International Classification of Diseases, Tenth Revision defines opioid dependence syndrome as a cluster of behavioural, cognitive and physiological phenomena that develop after repeated opioid use (WHO, World Health Organization, 1993). In 2018, there were 57.8 million people globally who were past year users of opioids. Ireland has a prevalence of around 6.18 per 1000 population accounting for 18,988 high-risk opioid users (EMCDDA, 2019).

In Europe, opioid use (predominantly heroin) is the main reason for people entering specialised drug treatment and represents 34% of all treatment requests (EMCDDA, 2020). As of March 2021, there were 11,445 people registered with the Central Treatment List in Ireland receiving opioid agonist treatment (OAT).

Integrated drug treatment programs combine pharmacotherapy with a range of medical and psychosocial interventions (HSE, 2016). OATs (primarily methadone and buprenorphine) are the gold standard pharmacotherapy in the treatment of opioid use disorders (Volkow *et al.*, 2019).

OAT is known to keep people in treatment, reduce illicit opioid use, reduce related risk behaviour and mortality and improve mental health. This impact may be enhanced with psychosocial support together (EMCDDA, 2017).

Oral methadone was introduced as the standard pharmacological treatment for the management of opioid dependence in Ireland in 1971, and it has remained the mainstay of treatment since (Delargy *et al.*, 2019). The introduction of sublingual buprenorphine in 2005 has offered a greater choice of treatment for problem opioid users in Ireland (Long, 2006).

Methadone is a full agonist of the mu opioid receptor, while buprenorphine is a partial agonist. As such, the risk of overdose is less with buprenorphine, particularly during the initiation phase (Kimber *et al.*, 2015). However, sublingual buprenorphine formulations have been linked to concerns regarding diversion, misuse and other harms associated with intravenous drug use (Lofwall *et al.*, 2014). Combinations of buprenorphine/naloxone have been developed to reduce this risk of abuse (Stoller *et al.*, 2001)

Methadone remains the first-line treatment of choice; however, there are certain circumstances whereby buprenorphine may be the preferred option. These include for patients with prolonged corrected QT-interval, patients treated for codeine dependence, patients who are in stable employment or education and patients diagnosed with HIV to facilitate alternative HIV treatment options (HSE, 2016). Recently, the numbers of people in receipt of buprenorphine as an OAT has increased due to a revised induction protocol developed during the COVID-19 pandemic, when the goal was to induct as many Opioid dependent people as possible onto treatment safely and quickly (HSE, 2020).

Oral methadone requires daily dosing while sublingual buprenorphine requires daily or alternate daily dosing. In the initial stages of treatment (i.e., induction and stabilisation), frequent supervised consumption is recommended (HSE, 2016).

Certain limitations and burdens that may be associated with conventional OAT include variable adherence, difficulty achieving optimal dosing, risks related to misuse, diversion and accidental exposure as well as stigma from the treatment process (Gilman *et al.*, 2018). The option of providing OAT using longer acting or slow release preparations has emerged as a viable alternative, and a number of services internationally are utilising this approach including in Australia and the UK (Larance *et al.*, 2019; Parsons *et al.*, 2020).

There are currently three different formulations of prolonged-release buprenorphine (PRB) worldwide – one subcutaneous implant (Sixmo) and two subcutaneous depot formulations (Sublocade and Buvidal) (Chappuy *et al.*, 2020).

Sixmo is a six-month buprenorphine implant that is surgically inserted into the inner part of the upper arm. Treatment is limited to two successive implants, that is, 12 months in total, after which point, the patient is switched back to the oral form. It has been shown to be at least as effective as sublingual buprenorphine and is stored at room temperature.

Sublocade is a monthly subcutaneous buprenorphine depot that has been approved for use in the USA but not yet in the EU. There are two available monthly doses – 100 or 300 mg. It must be stored in a refrigerator (at between +2 and +8 °C) as its stability does not exceed seven days at room temperature.

Buvidal is the first PRB depot formulation that has received a European licence. It is available in weekly (8, 16, 24 or 32 mg) or monthly (64, 96 or 128 mg) doses

and is stored at room temperature. The European Medicines Agency has concluded that Buvidal is at least as effective as sublingual buprenorphine at treating opioid dependence and offers an additional treatment option (EMA, 2018).

For patients, potential benefits of PRB formulations include reduced stigma, improved quality of life and more time available to complete other activities of living (Gilman *et al.*, 2018; Neale *et al.*, 2018; Tompkins *et al.*, 2019). Participants from both an Australian and a UK sample reported perceived benefits of preventing opioid cravings and suppressing withdrawal symptoms for prolonged periods (Larance *et al.*, 2019, Tompkins *et al.*, 2019).

Of those who have had experience with Buvidal in the UK, there have been positive reports across areas of treatment effectiveness, convenience and overall satisfaction. The majority of the group reported specific benefits of reduced cravings, improvements in self-care and relationships and a more positive outlook on life (Parsons *et al.*, 2020).

A recent Australian open-label randomized control trial showed that patient-reported outcomes, such as treatment satisfaction with medication were significantly higher among patients treated with depot formulations of buprenorphine compared with sublingual buprenorphine (Lintzeris *et al.*, 2021).

Buvidal is the first and currently the only PRB formulation that is available for use in Ireland. Treatment has been commenced on a pilot basis with a cohort of opioid dependent patients who are attending the HSE National Drug Treatment Centre and certain addiction services within the Dublin North County and City area. Initial reports seem positive. Longitudinal results and findings from this study are eagerly awaited to determine whether this is a viable option to expand treatment options in Ireland.

The Covid-19 pandemic presented specific challenges for addiction services in Ireland (Hennigan *et al.*, 2021). The availability of a prolonged release medication for OAT would have been of benefit in reducing attendances at addiction clinics and general practitioner surgeries and enhancing compliance with public health guidance on travel. This, in turn, would have resulted in additional safety measures and improved health outcomes for this vulnerable population.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

Authors have no conflict of interest to disclose.

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https://doi.org/10.1017/ipm.2021.62 Published online by Cambridge University Press