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"Bursting the Lyrica bubble": Experiences of pregabalin use in individuals accessing opioid agonist treatment in Dublin, Ireland

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Summary

Background: Pregabalin, also known by a brand name of Lyrica, is a prescription only gamma-aminobutyric acid (GABA) analogue and licensed for a range of medical conditions, e.g. chronic pain, generalised anxiety and epilepsy. In recent years, pregabalin has attracted clinical and research attention due to an increase in its association with overdose fatalities. Individuals with opiate use and those in opioid agonist treatment are an identified at risk group for problematic pregabalin use and overdose. As such, research focusing on pregabalin use in individuals accessing opioid agonist treatment is highly relevant. **Aim:** This study aims to add to the evidence based on diverted pregabalin use in the OAT cohort in Ireland. **Methods:** Fifteen semi structured interviews were conducted and analytically coded using thematic analysis with software programme NVivo12. **Results:** Individuals on OAT may use Lyrica to self-regulate negative emotions; Lyrica use in this population is embedded in a polydrug use culture of "tablet taking"; participants illustrated concerning reports of inappropriate prescribing and described psychiatric symptoms occurring during withdrawal. **Conclusions:** We report here on the first study in Ireland investigating the experiences of individuals who access opioid agonist treatment (OAT) and reported current or recent pregabalin use. Increased pharmaco-vigilance amongst medical practitioners is warranted when prescribing Lyrica to individuals with vulnerabilities such as a history of problematic drug use. Trauma informed interventions in addition to pragmatic harm reduction information for polydrug users to prevent cross tolerance, dependence and overdose deaths should be part of the healthcare and policy response.

Key Words: Pregabalin; Gabapentinoid; Lyrica.

1. Introduction

Pregabalin, also known by a brand name of Lyrica, is a prescription only gamma-aminobutyric acid (GABA) analogue and licensed in different jurisdictions for a broad and diverse range of medical conditions e.g. neuropathic pain, fibromyalgia, generalised anxiety and epilepsy [27]. Pregabalin was made a controlled drug in 2005 in the United States [27] and in 2017 in the United Kingdom [43] due to recognition of its abuse liability. A central nervous system depressant, pregabalin was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Early Warning System in 2009 [11]. Since then, European prescribing rates have increased, and with increasing concerns around misuse, dependence and pregabalin related overdose deaths in certain countries (Germany, Finland, Sweden and the United Kingdom) [27]. Pregabalin has attracted attention in Ireland where our study took place, with a marked increase in its association with overdose fatalities – from 14 to 65 in Ireland between 2013 and 2016 [27, 32, 33]. Contributory to such overdoses is the consumption of much higher doses than typically prescribed in order to produce psychoactive effects such as euphoria, relaxation and disassociation [2, 27, 37]. Notably, pregabalin has been shown to reduce opiate withdrawal symptomatology and to enhance the psychoactive effects of opiates [32]. In this regard, individuals with opiate use and those in opioid agonist treatment (OAT) are an identified at risk group for problematic pregabalin use [29, 32,

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36]. Recently, an Australian study of toxicology databases [4], a US register based study [1] and a UK analysis of drug screening results [26] have contributed evidence that polyuse of opiates and pregabalin carries an increased risk of fatal overdose. As such, research focusing on pregabalin use in individuals in OAT is highly relevant. Both opiates and pregabalin stimulate central nervous system depression, causing sedation, respiratory depression and death [3]. Pregabalin is misused at supra-therapeutic doses with bioavailability increased when combined [3].

Prevalence of pregabalin misuse among OAT patient's ranges between 3% to 68%, and with higher prevalence of misuse reported among psychiatric patients and prison inmates. People who use pregabalin experience tolerance and subsequent withdrawal symptoms on cessation [3]. Dependence mechanisms are not yet well understood. Published empirical research on pregabalin use in Ireland is limited to two studies: one which analysed drug screening results of individuals in the addiction services [29] and a single case study focusing on reported libido enhancing effects [30]. Two editorials highlight concerns related to increasing pregabalin misuse in the Irish context [5, 27] which mirror those of international authors. Currently, little is known about patterns of pregabalin use in individuals who access OAT including motivators for use, sourcing routes and side effect profiles. A need for continued research in this area has been highlighted by Irish researchers [5, 27, 29, 30]. This paper reports on the first study in Ireland to investigate the experiences of individuals who access OAT with pregabalin use.

Aim: This study aims to add to the existing evidence base and to further national discussion on how to improve our healthcare and policy response to this emergent trend and associated risks.

2. Methods

Ethical approval for the study was granted by the Liverpool John Moore's University Research Ethics Committee (UREC), United Kingdom (19/PHI/005). A qualitative descriptive study was conducted using semi-structured interviews (SSIs) with 15 individuals accessing OAT in an area of Dublin. This service provides OAT as well as other essential harm reduction services. A semi structured interview guide was developed based on two studies conducted by author two [2, 3] on diverted pregabalin use and included topics such as motivators for use, polypharmacy patterns, side effect profiles, views and perceptions of risk and sourcing routes. Participants were recruited through recruitment posters and via a gatekeeper at the service during January and February 2019. The gatekeeper signed a confidentiality agreement with the research team in protection of the identity of the participants. Eligibility criteria included that the individual was either currently or previously on an opioid agonist programme and had either current or recent pregabalin use. Exclusion criteria referred to those who had no pregabalin use and to individuals who, due to intoxication or other circumstances, a service gatekeeper determined as having compromised capacity to consent to the research.

2.1. Data collection

One member of the research team interviewed participants in a private room at the service between March and June 2019. Each interview took approximately 45 - 60 minutes. All participants were read a statement of consent which outlined all relevant information pertaining to the study. Participants gave verbal consent to participation in the study. All participants agreed to be audio recorded. They were assured all personal identifiers would be removed in order to ensure confidentiality. Participants were informed of the availability of a counselling service for any individual should they become distressed or affected by the topics discussed at interview, and of their right to revoke their consent to interview at any time without recourse.

2.2. Data analysis

Audio recordings were transcribed verbatim. Data was analysed using applied thematic analysis [16]. Transcripts were read by both research team members. Based on the literature review conducted and the interview guide used, a preliminary thematic structure was developed as the researchers familiarized themselves with the data and sorted it under overarching emergent themes. Coding was aided by use of NVivo12 software. This initial thematic structure was advanced as each researcher coded an individual transcript and indicative themes emerged from the data. To establish intercode reliability, discrepancies in coding were discussed between both team members and further codebooks (N=2) developed. All transcripts were revisited with the final codebook and the data interrogated using the final thematic framework. In the ethos of participatory research, once data was coded, author one visited the service during October

2019 and conducted a "participant check" [24]. Research findings were presented to participants one to one and confidentially, and feedback was sought to ensure that their authentic voices were accurately represented in the author's interpretations.

3. Results

15 individuals partook in the interviews, with ages ranging from 25 to 45 years (nine male/six female). Twelve of these were currently accessing OAT and three had transitioned from treatment. Lyrica was the common drug used when referring to pregabalin.

3.1. Lyrica use patterns, motivators for use and side effect profile

Half of all participants reported being initially prescribed Lyrica legitimately for, mainly, pain related conditions. Problematic use and increases in amounts developed rapidly for OAT participants in this category, who described motivators for using supra-therapeutic doses as enhanced sociability; reduced anxiety; increased confidence, and relief from emotional distress. The remaining half of participants reported their first use of Lyrica as diverted medication occurring through peer networks. For many participants Lyrica use was embedded in a polydrug use culture of "tablet taking", where diverted prescription medication such as benzodiazepines, z-hypnotics and painkillers were used, either daily, in isolation or socially. For some, a longstanding relationship with "tablets", such as diazepam, had led to the initiation of Lyrica use. The self-regulation of negative emotions through Lyrica use was noted in OAT participants. A substantial evidence based exists on the use of illicit substances to regulate emotions and to cope with past trauma and life stressors [7, 20, 21, 42, 44]. In the following illustrative quotes, Lyrica was described as a coping strategy:

"They say a high, but tablets don't give you a high. It's just a relaxed, fuck everything kind of feeling. Forget about all that. You don't have to deal with that until tomorrow…or next week…whatever. That's why I do it cos most things, I don't want to deal with. I can't even handle that shit. Do you know what I mean?" (Participant 2, female).

"They numb the shit, the pain that you…the loss. They knocked all that out." (Participant 4, female)

"It was prescribed to me for pain. It was given to me then. I didn't know about the buzz out of them. I didn't even read the leaflets. It was just given to me for pain relief. It stopped the pain in my knees. But then I started overtaking them and I was getting that false confidence. That's what I take them for...that false confidence…I'm able to be out there. Without them, I'm in my shell….I'm taking them to be a false me. I have issues that I haven't dealt with." (Participant 9, male)

Indications of self-regulation of negative emotions with increasingly larger doses are also consistent with the findings of a single case report of a male diagnosed with pregabalin use disorder [35].

As documented previously [5], the physiological effects of Lyrica were described as comparable to alcohol intoxication: "when you're in that Lyrica bubble, it's like you're buckled drunk" (participant 1, male). For that reason, few participants reported drinking alcohol when consuming Lyrica. The consumption of large dosages already noted in the literature [13] was also seen in this study, and ranged from 800 mg daily (prescribed dose) to an incident of ingestion of 6000 mg in one episode. Many participants reported dosages in excess of 1000 mg daily. One participant described his experiences of overdosing twice on Lyrica:

"I overdosed twice. The first time I OD'd they gave me charcoal……the second time, I went blue and I ended up getting pneumonia and that. That snapped me out of it, and I said I'm not taking them like that… so I went up to the doctors. When my mate saw me in the hospital when I died...he said, "I'm never giving you them again". (Participant 7, male).

Routes of administration were largely oral, swallowing or chewing, with insufflation also reported by some. While some participants reported knowledge of injecting use by peers, all stated injecting was something they would not return to, due to its association with past problematic heroin use. Delayed effects, prompting re-dosing, were reported, perhaps due to procurement of a type of controlled release Lyrica called GLA5PR GLARS-NF1 [40]. Undesirable side effects described included loss of consciousness; vomiting; loss of control and out of character behaviours such as shoplifting, and aggression attributed to feelings of invincibility:

"It's got me into a lot of trouble. I've had a few charge sheets. From…when I take them, I forget, like that I feel like I'm invisible, I do more stuff. I've been fighting…They're mad they send you off your head" (Participant 12, female)

"When you're on the tablets like, you think you're invincible, that no one can see you…last time I was on Lyrica I got a charge sheet…I thought people

were winking at me and letting me take things (shoplift) …and then I get caught" (Participant 2, female).

3.2. Sourcing

A combination of legitimate and illegitimate sourcing routes and displacement between these routes were described. In participants who initiated their Lyrica use through a doctor's prescription, many transitioned to street sourcing to supplement their prescribed use. Conversely, some participants who initiated with "street" use transitioned to prescribed use. As seen in a number of population groups with problematic use of prescribed benzodiazepines and opioids [15, 39], some participants reported drug seeking behaviours such as exaggeration of symptoms; visiting multiple doctors or "doctor shopping" (seen also in studies of pregabalin use [4, 9]). Diversion of the prescriptions of family and friends and attempts at prescription forgery in order to obtain Lyrica were also described. While there were some reports of careful assessment by doctors, where participants found it difficult to obtain Lyrica, there were also a number of concerning reports of obtaining Lyrica from doctors and pharmacists illegitimately, a rogue practice documented, for example, in the case of prescription opioids in the US [39]. Cash sales of Lyrica have also previously been documented in a minority of pharmacists in Jordan, Egypt [2]. Inappropriate prescribing by general practitioners was also described by participants:

"I know of doctors who if you slip them fifty quid, they'll give you Lyrica…meet you in the carpark…whatever." (Participant 1, male)

*"I'm a regular for going back to the doctor early and he used to be grand....I would be going' back every ten days instead of every two weeks and he would always give it." (*Participant 4, female)

An additional sourcing route described by one participant was through social media site Face Book, where an unknown seller would initiate contact through a friend request and accept payment through Western Union. The selling of controlled substances through social media has been documented previously [8, 41].

3.3. Dependence and withdrawal

Consistent with previous reports [4, 35, 38, 46] ,indications of dependence symptomatology (e.g. tolerance and withdrawal) were illustrated in some participant's narratives:

"They're ruling my life like. They are ruling my life. I won't go anywhere without…" (Participant 4, female)

Withdrawals from Lyrica were described by a number of participants, many with prior experience of withdrawing from opiates, as remarkably severe. Recently, Schifano and Chiappini [37] highlighted that a research lacuna exists in documenting the experiences of individuals after detoxification who had voluntarily sought help for dependent use of pregabalin. One participant in our study, no longer using Lyrica, describes how he self-detoxified at home:

"It wasn't a slight... withdrawal. It was horrible. I couldn't hold anything in my body. If I wasn't crying, I was throwing up. I had no energy at all. I was basically crying the whole way through. It was horrific. Going from the bathroom to the bed. I'd never felt like that before. When I was going through withdrawals from methadone, I was able to eat. I was still able to do all that. (With Lyrica) I was like that for about nine days... the effects on my head lasted way longer… at least a month. I was paranoid, I felt I had no worth." (Participant 6, male)

Another participant sought help with dependent use of "street" sourced Lyrica through a supervised medical detox:

"Then I got them prescribed from my doctor…I asked him to detox me. He didn't want to, but I said if you don't give them to me, I'm gonna die off them. I needed them I was addicted to them. I was on three a day for a couple a month, then two a day for a month and now one a day. I get them takeaways twice a week. I give him to my ma; she leaves one a day on the locker for me with my methadone. I'm finished next week." (Participant 7, male)

A single case study published in 2018 [17] details a first episode of psychosis attributed to pregabalin withdrawals where the patient suffered paranoia, hallucinations, self-harm and suicide. Similar psychiatric symptoms were described by participants in this study when discussing their withdrawals from Lyrica:

"Cold turkey. Don't ever try cold turkey. It's like dying sick from other tablets...the only difference really is the psychosis part of it...you don't fit in your skin…you're on a weird type of buzz like. You're agitated, you're overstressed, your fear, it's ten times worse. You won't talk to people. Lyrica is different that way, the psychosis is worse." (Participant 8, male)

"The withdrawals…and then it's kind of like, a bit of psychosis in the head like...you'd find yourself sitting there and you're actually having a conversation with yourself in your head… I just lock myself in,

I might as well be in a prison cell. I can feel the walls closing in… I have a big fear of just dropping them. I did try drop them…and I nearly went off my head. I had to go back to my doctor and lie to him straight away. I got ten days out of it. I was emotional…suicidal. I couldn't even talk." (Participant 9, male)

3.4. Polydrug use repertoires and Lyrica intersection with opioids

As documented in previous studies [6, 12] Lyrica use was situated within habituated polydrug use practices for many participants, which included prescribed and "street" use of methadone, benzodiazepines, z-hypnotics and also use of stimulants such as crack cocaine and "snow blow", a synthetic cathinone. Use of Lyrica, a CNS depressant, to "come down" from stimulants was reported by some participants, in addition to concurrent use to enhance the effects of other substances, as illustrated by this quote from a participant speaking about using crack cocaine and Lyrica together:

*"It's like a hybrid. It's pleasant…it calms…but you've still got a little bit of the crack going on in your brain as well… and then you've got the Lyrica coming in to counter it, it's like balancing the scales" (*Participant 1, male)

To date, researchers have not been able to pinpoint exactly why pregabalin misuse is popular among individuals with opioid use [37]. The data from this study agreed with previously documented findings [12, 26] on the ameliorating effects of Lyrica on opiate withdrawal syndrome:

"Better than Zimmovaines or D10s (diazepam), Lyrica will hold you until the next morning" (Participant 10, female).

Moreover, one participant reported using Lyrica legitimately to aid with his methadone detox. However, more nuanced comparisons were made between opiate use and Lyrica use by some participants who recalled a similar relationship to heroin at one point in their lives:

"You know what it reminds me of? Using gear back in the 90s…scamming money...do you know what I mean... If you don't take them like, first thing my leg starts going and that reminds me of gear, straight away. Then the back, and then the skin. It's like being sick off gear. It's taking over you. It's a hundred percent like it." (Participant 9, male)

One study suggested that high tolerance to substances after long-term opioid use may cause an inclination to use newer drugs such as pregabalin [14]. In line with this theory, two participants suggested that due to the strong effects of Lyrica, many people without problematic drug use would not be as likely to use them:

*"I think mostly its people in addiction. People who just take (drugs) here and there…I can't see them liking them. They're so strong... unless I had another habit, I wouldn't like the feeling of it. Whereas because I already had a tablet habit, I was able for it." (*Participant 6, male)

"You'd have to take heroin or foy (methadone) or stuff like that. To be able to handle it." (Participant 11, male)

3.5. Perceived harms and harm reduction strategies

Risk perceptions were centred on the fear of overdose, as seen previous research [26] and which was largely due to local and communal knowledge of fatalities or negative personal experiences:

"My best mate died of Lyrica only three or four years ago …she had Lyrica, drink, gear (heroin) ...a load of different things. When I go to bed, I think of that…. I think all drugs are the same, but I just hear of more deaths from Lyrica. I think that people are mixing them….and like me I just kept swallowing and swallowing and swallowing…. my heart was thumping, I had to open the window and breathe properly and calm down." (Participant 2, female)

Indigenous harm reduction measures were seen in the data where participants described the avoidance of counterfeit Lyrica through only purchasing those that were encased in foil sheets (as opposed to loose tablets); asking questions about whether the Lyrica came from a chemist and reducing their own use:

"I had a bad experience. I will not buy street tablets. I took fake Trannex and collapsed and was in (name of hospital) for three weeks. If I'm buying tablets, I have to see them in the wrapper. And the dates...I go that far I check the dates. I know the cards…I know the shape of the card. I'll pop it out of the thing… and I'll know how far the colours go." (Participant 9, male)

4. Discussion

We present here the findings from the first qualitative study in Ireland to explore pregabalin use from the perspectives of Irish OAT patients, which are identified in the literature as a key user group. Analysis of the current trend for high dose Lyrica use in this population and potential responses may be conceptu-

alised using a socio ecological model (see **Figure 1**) which considers individual, community and systemic factors creating a risk environment unique to time and space [34].

Causal factors in the significantly higher rates of problematic pregabalin use amongst the OAT population have been documented in the literature, e.g. to relieve opioid withdrawal syndromes or enhance the effects of opioids [12, 26] and due to its potent intoxicating effects [14]. The data from this study agreed with such previous findings, and also draws a comparison between the descriptions of pregabalin use by participants and the hypothesis of self-medication theory [20, 21]. Self-medication theory posits that problematic substance use is grounded in the relief of "distressing psychological symptoms" [7]. Many participants described using Lyrica to "cope" with feelings of anxiety or loss. There is a strong association between OAT patients and trauma [28, 45] which may include a multiplicity of adverse childhood events (ACEs) [31]. In this regard, trauma informed interventions, practices and services [22] would be a valuable approach in responding to the needs of OAT patients using pregabalin drugs, such as Lyrica. Trauma informed practices include training for staff and adaptation of the clinical environment to support emotional regulation in service users. Our study contained reports of psychiatric symptoms in individuals withdrawing from pregabalin use, including anxiety, depression, hallucinations and suicidal ideation. Individuals in OAT are particularly vulnerable to self-isolation and feelings of depression [28]. Pregabalin withdrawal syndrome should be considered as an additional risk factor for acute psychiatric symptoms including suicidal thoughts by medical professionals and service providers. Awareness amongst service providers around the potential for "home detoxification" where individuals may become vulnerable, isolated and unwell is warranted, so that those who wish to stop their pregabalin use can be supported to do so in a safe and medically supervised way if necessary.

Polydrug use is an area of public health concern and has also been described as "the norm" in drug using populations [19]. For most participants, as seen in previous research [6, 12] pregabalin was embedded in polydrug use repertoires. Again, polydrug use is associated with trauma [18] and individuals may access a range of substances to regulate their emotions. In addition to the recommendations already made with regard to trauma informed care, an efficient healthcare response to polydrug use should be focused on the delivery of pragmatic harm reduction information around potentially lethal combinations and reduction of amounts. One finding of our study was that participants may be unwarily accessing a type of controlled release pregabalin which heightens re-dose potential. Awareness needs to be raised around re-dosing risks specific to this finding. Participants in our study ex-

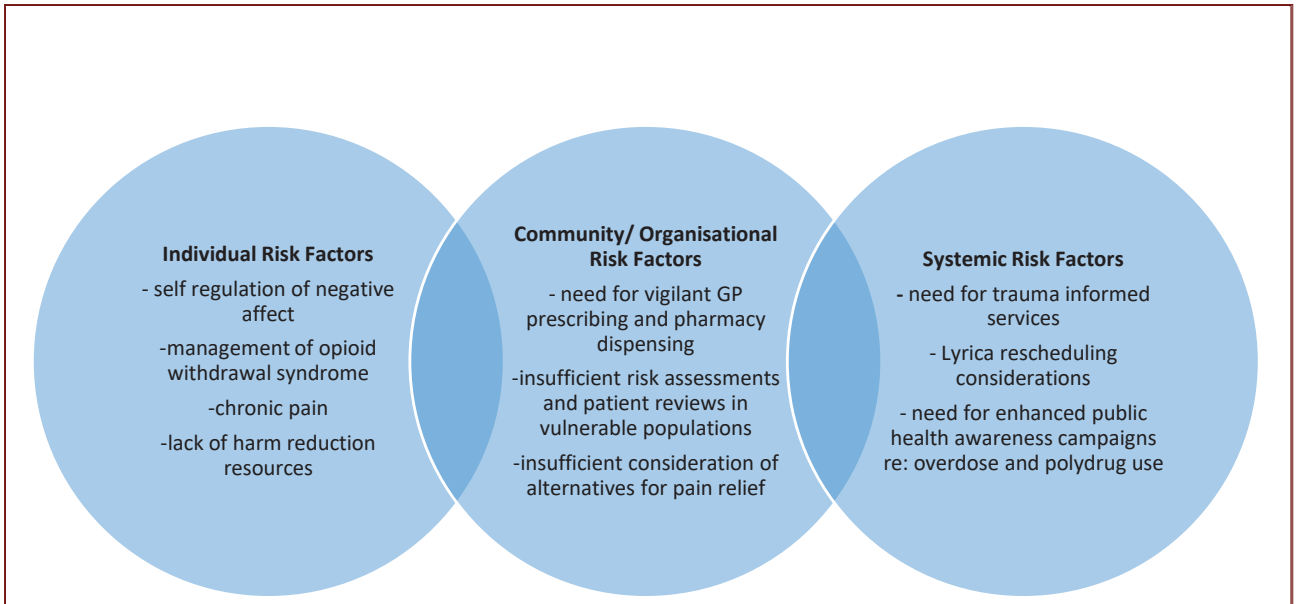

Figure 1. The risk environment for problematic Lyrica use in the opioid agonist population in an area of Dublin, Ireland

hibited indigenous harm reduction practices in order to protect their safety and wellbeing when describing measures taken to avoid procurement of potentially dangerous counterfeit tablets. Harm reduction programmes recognize that individuals with drug use are autonomous in adjusting their use when properly informed and supported to do so. The reduction of heavy polydrug use to moderate use is a worthy one and is associated with less risk behaviours [25]. Tailored brief interventions that are contextually appropriate to the in-treatment population with pregabalin use must be developed and implemented in services.

The risks incurred by Lyrica use in this population do not occur in isolation, but rather are situated in a unique risk environment influenced by local structural factors [34]. Since the 1970s, people who polydrug use have substituted substances in their repertoire according to availability and fluid drug trends [10]. Pregabalin is currently being prescribed to individuals in OAT in Ireland. While one participant felt that pregabalin was helping him detox from methadone, the majority of participants in this study expressed regret at being introduced to pregabalin drugs: "I wish I never knew about them" (Participant 13, female). This was seen in participants' narratives as being due to quick building tolerance, the severity of the associated withdrawal syndrome and fears around overdose. While examples of good practice by general practitioners were illustrated where participants described finding it difficult to be prescribed Lyrica or have their doses increased, extraordinary claims of purchasing Lyrica for cash from doctors or pharmacists and accounts of inappropriate prescribing were also evident. In light of the evidenced increased risk of overdose [1, 4, 26], medical professionals need to be vigilant when prescribing pregabalin to vulnerable individuals, including those with a history of problematic opioid or other depressant medications, and those currently on OAT. Alternatives must be considered, alongside tailored risk assessments and regular reviews of patients, and the avoidance of off label prescribing. Increased attention to the diversion of prescriptions is also warranted and a scaling up of harm reduction programmes with Lyrica (and other gabapentinoids) overdose education. Increased monitoring of Lyrica prescriptions through an interagency prescription drug reporting programme may be required. Consideration might also be given to the rescheduling of Lyrica as seen in the UK, the US and in Norway. In addition to prescribed use, Lyrica is also situated in a "street" use risk environment shaped by the availability of counterfeit tablets with potentially dangerous consequences for people who take them. Although many participants were resourceful in developing strategies to protect themselves from the procurement of counterfeit Lyrica, harm reduction programmes should contain safeguards in recognising illicitly manufactured and counterfeit drugs.

The main limitation of this study is that its small sample size and localized nature does not allow for generalisation. The data is also self-reported and may be subject to recall bias, particularly in recollections of overdose. However the reliability of self-report measures in people who use drugs has been validated previously [23]. Due to the nature of polydrug use, causal inferences cannot be made about the effects of Lyrica. However, we interviewed a range of individuals of both genders, with authentic accounts of polydrug use with Lyrica and other substances, which contribute valuable insight into their experiences. We are unaware of any other Irish study prior to ours to document qualitative evidence of the experiences of pregabalin in the in-treatment population.

5. Conclusions

We found that pregabalin (Lyrica) use in individuals accessing OAT in an area of Dublin, Ireland was associated with self-regulation of negative affect; a combination of legitimate and illegitimate sourcing routes and severe withdrawal syndrome including psychiatric symptoms. Increased general practitioner and pharmacist vigilance in relation to prescribing and dispensing of Lyrica and enhanced risk assessment protocols when responding to presentations for pain relief are needed. Trauma informed practices in services and increased delivery of tailored drug specific and polydrug harm reduction information to prevent overdose in this high-risk group is recommended.

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Contributors

R.B., designed the study and wrote the protocol. R.B., managed the literature searches and analyses. R.B., M.C.V.H., undertook the statistical analysis, and all the authors discussed the results. R.B., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

All authors have no conflict of interest.

Ethics

Ethical approval for the study was granted by the Liverpool John Moore's University Research Ethics Committee (UREC), United Kingdom (19/PHI/005).

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