Withdrawal, dependence and adverse events of antidepressants: lessons from patients and data

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Tolerability, withdrawal effects and dependence on prescription medication is an important topic of current scientific and clinical debate, as highlighted by the recent report published on September 2019 by Public Health England (https://www.gov.uk/government/publications/prescribed-medicines-review-report).[1] This was a mixed methods public health review of available evidence in adults focusing on specific issues of dependence and withdrawal associated with five groups of medications: (1) benzodiazepines, (2) z-drugs, (3) gabapentin and pregabalin, (4) opioids and (5) antidepressants. The evidence included in the review consisted of: General practitioner (GP) patient data (real-world data), community prescription data in England reported during 2015–2018, longer-term prescription cost analysis data from 2008 in England, and a rapid evidence assessment of published and unpublished literature, including randomised and observational studies. The grey literature was used mainly as a source of information on patients' experiences. Retrieved information was carefully appraised and the review findings were given a level of confidence using the GRADE-CERQual framework (https://www.cerqual.org/). In the report, three different inter-related entities were considered: *dependence* was defined as 'an adaptation to repeated exposure to some drugs or medicines usually characterised by tolerance and withdrawal….' (p8), *tolerance* as 'neuroadaptation arising from repeatedly taking some drugs and medicines, in which higher doses are required to achieve a desired effect' (p8) and *withdrawal* as 'physiological reactions when a drug or medicine that has been taken repeatedly is removed' (p8).

Results about antidepressants are reported on pages 41–115.[1] With 71 million prescriptions being issued, 7.3 million people (17% of the adult population) were prescribed antidepressants in 2017–2018, increasing from 6.8 million (15.8% of the adult population) in 2015–2016. Basically, one in six adults in England had an antidepressant prescription dispensed in 2018. The review also reported that approximately 21% (940 000 people) of 4.48 million in receipt of an antidepressant prescription in March 2018 had been taking antidepressant medication continuously for at least 36 months. Interestingly, 12% of people (approximately 520 000) received an antidepressant prescription for less than 1 month. Overall, antidepressants were not associated with a significant risk of dependence; however, they were associated with withdrawal symptoms, including insomnia, depression, suicidal ideation and physical symptoms (see report for full details).

As clinicians prescribing antidepressants, we need to be aware of the importance of adverse events for decision making.[2] Individual side effects (including withdrawal symptoms) are extremely impairing to patients,[3] and involving them in the decision making is the key. We are in the process of analysing the data from SUSANA (Survey for Understanding the Side effects of ANtidepressants in Adults (http://clinicalepidemio.fr/proceed2/en/)). This is an international survey about side effects of antidepressants in depression, which has been carried out in English, German and French and has collected feedback from more than 2000 patients, carers and clinicians across the world.[4] SUSANA is part of a larger project supported by the UK National Institute of Health Research (NIHR) and the NIHR Oxford Health Biomedical Research Centre, which is called PETRUSHKA (Personalise antidEpressant TReatment for Unipolar depreSsion combining individual cHoices, risKs and big datA). PETRUSHKA rationale and protocol is published in this issue of the journal[5] and it aims to integrate the best available scientific information with the preferences of patients and clinicians to provide, for the first time, an evidence-based bespoke clinical decision aid to tailor antidepressant treatment in primary and secondary care within the national health system. SUSANA focused specifically on the most common/frequent adverse events, but it also provided patients and clinicians with the opportunity to describe their experience of adverse events, especially if less common or more severe. Here are some examples of how anonymous patients report the experience of withdrawal symptoms:

> I found that the withdrawal effects were too easy to misinterpret as mental illness, and this placed me on a treadmill of re-prescribing
> … coming on and off antidepressants for 6–12 months at a time without sensible tapers over months rather than weeks set me up for more psychiatric problems and physical symptoms than I would have thought possible…
> For several months coming off of them I felt depressed and agitated, dizzy … My GP did not tell me that this might happen, so I thought I needed them to feel okay and went back on them.

These examples illustrate the need to facilitate access to evidence-based updated information about the effects of treatment interventions[6] and to involve patients more in their day-to-day care, with a focus on carefully acknowledging the risk and outlining potential side effects while managing expectations. Monitoring adverse events is challenging in clinical trials and even more in the real-world setting. In routine clinical practice, adverse event recording is largely dependent on

Announcement

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the clinician and the willingness of patients to report them. The evolving landscape of digital technology and devices available to healthcare professionals and patients could potentially transform the ways that clinicians manage conditions and adverse events.[7] At the same time, the development of artificial intelligence-based technologies in medicine is advancing rapidly, but real-world clinical implementation has not yet become a reality.[8] There are key practical issues about the implementation of artificial intelligence into existing clinical workflows, including data sharing and privacy, transparency of algorithms, data standardisation, interoperability across multiple platforms and concern for patient safety. This is the way to go and population-based registries should adapt and evolve to accurately capture all the clinically relevant information. Scandinavian countries have a strong track record in the field, but probably the UK is in a better position for primary care (for instance, QResearch—www.qresearch.org/ or Clinical Practice Research Datalink—cprd.com/home) and also for mental health (UK Clinical Record Interactive Search—crisnetwork.co/uk-cris-programme), with a huge potential in cross-linking these different databases. Accurate and transparent reporting of adverse events in the scientific literature and high-quality real-world data sets is imperative to provide healthcare professionals with the information to enable an informed risk-benefit decision of medication.

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