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Need for evidence-based approach to benzodiazepine dependence in opioid agonist treatment

PERSPECTIVES

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When repeated attempts to taper benzodiazepines are unsuccessful, clinicians face a dilemma: should the ideal of recovery remain the goal?

Patients attending opioid agonist treatment (OAT) clinics in Norway often struggle with anxiety, insomnia, trauma and withdrawal symptoms. Many have used benzodiazepines for a long time, often at high doses and obtained illegally. Tapering is often attempted without success. Nevertheless, there is considerable clinical and ethical uncertainty about whether some of these patients should be offered a stable, prescribed treatment for benzodiazepine use.

The issue is controversial. Benzodiazepines are associated with dependence, cognitive impairment and an increased risk of overdose, particularly when combined with opioids (1–3). However, a large proportion of OAT patients use these medications regardless of whether they are prescribed or not (4–7). The

difference is that the strength and composition of illegal substances are unknown, their availability is unpredictable and they carry a higher risk of poisoning and fatal overdose (8–12).

A study of a Norwegian prescription database shows that approximately half of OAT patients were prescribed benzodiazepines at least once during the study period (6), and overall, up to two-thirds likely use such substances, either prescribed or illegally obtained (4, 5, 7, 13). In recent years, prescription numbers have increased, while reported illegal use has declined (4). This may partly reflect the implementation of revised national guidelines for the treatment of opioid dependence, which allow for maintenance treatment with benzodiazepines in exceptional cases with a view to reducing risk and improving quality of life. However, the efficacy and safety of this approach are not yet documented (14, 15).

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Behind these figures is a patient group with a high burden of disease, widespread psychiatric comorbidity and often a long-term substance use disorder (SUD) (13, 16). Benzodiazepines are often a central part of everyday life; alleviating withdrawal symptoms, anxiety and agitation, and enabling sleep. Cessation of these medications can lead to marked functional decline, reduced quality of life, increased substance use, or a transition to more harmful substances.

High-potency benzodiazepines such as clonazepam and alprazolam predominate on the illegal market, alongside an increasing presence of designer benzodiazepines and combination products that may contain potent synthetic opioids (8–12). It is no coincidence that those purchasing 'street pills' prefer high-potency agents that offer 'better value for money'. However, this can also draw users further into drug-using communities, acquisitive crime and drug dealing to fund their own use. The associated health risks for those involved, and the broader societal implications, are therefore substantial and extremely challenging to manage – both clinically and from a public health perspective.

The ideal and the reality

Management of benzodiazepine dependence generally aims to minimise use, typically through tapering and cessation (14). This approach is based on the recognition that long-term use carries a substantial risk of harm and that gradual dose reduction is effective for some patients, particularly when combined with psychosocial therapy (16). However, clinical experience and data indicate that tapering is not feasible for all patients (16, 17), as repeated attempts are unsuccessful in some despite close and appropriate follow-up.

This raises the question of whether the ideal of recovery should remain the goal, even when it results in continued use of higher-risk illicit substances for many, or whether a more pragmatic harm-reduction approach should be considered, as provided for in current guidelines (14). Existing recommendations allow for both strategies, but this flexibility has led to non-uniform practices. Many clinicians working in OAT experience substantial clinical and ethical pressure when making treatment decisions (15), which can also lead to variation in prescribing practices among general practitioners (GPs).

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What is most risky?

Concurrent use of benzodiazepines and opioids is associated with increased mortality (2). However, the evidence base is limited regarding which is most risky: a stable, carefully monitored prescription regimen within OAT, or unpredictable illicit use while receiving treatment or after dropping out (2, 17).

The available studies are mainly observational, conducted in a variety of settings and have methodological limitations (2). Some data also suggest that cessation of long-term benzodiazepine use may increase the risk of overdose, suicide attempts and acute hospital admissions (18). The evidence is strongest regarding the relationship between mortality risk and dropping out of OAT (19).

This does not mean that prescribing benzodiazepines is without risk, but it serves as a reminder that cessation can also have unintended and serious consequences. An important point, therefore, is that absence of documented benefit is not evidence that prescribing benzodiazepines is harmful for all patients.

Harm reduction is not resignation

Harm reduction has long been an established principle in the treatment of SUDs. OAT is a good example of this: we recognise that complete abstinence from opioids is not realistic for all patients and adopt an approach (OAT with buprenorphine or methadone) that has a documented effect in reducing mortality and improving quality of life among heroin addicts (19). The question is whether the same principle should, in some cases, also apply to benzodiazepine dependence.

Arguing for this approach by no means trivialises the risk. On the contrary, it requires careful, individualised assessment of expected benefit versus potential risk, based on strict patient selection, clear treatment goals, a defined

framework, close monitoring and continuous reassessment (14). For some patients, tapering will remain the goal, but for others, the alternative to maintenance treatment may be considerably more risky.

There is general consensus that benzodiazepine dependence is a challenging clinical problem in OAT (1–3). The question is whether an overly restrictive approach may exacerbate the situation, prompting patients to turn to more potent and unpredictable substances purchased illegally (8–12). For particularly vulnerable patients, we should therefore consider whether a stable maintenance treatment may represent the lesser of two evils, while also improving quality of life. This is not a rejection of the ideal of recovery, but an acknowledgement that the path to it is not the same for everyone.

A better evidence base is needed

What is most striking in this discussion is how limited the evidence base actually is. To date, no high-quality randomised controlled trials have been conducted that provide clear answers as to whether maintenance treatment with benzodiazepines within OAT is safer or riskier than tapering for patients with long-term dependence (2, 17, 20). An ongoing multicentre study in Norway is investigating this question (21). The results will, hopefully, provide a more robust basis for future recommendations. Until then, clinicians will have to base their decisions on limited data, but harm reduction should be an integral component of individualised assessments.

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