

Review

Addressing the Issue of Chronic, Inappropriate Benzodiazepine Use: How Can Pharmacists Play a Role?

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Abstract: Prescribing guidelines do not recommend the long-term use of benzodiazepines since their effectiveness with chronic use is out-weighed by risks including dependence, memory and cognitive impairment, hip fractures and traffic accidents. Despite these guidelines, historical data points to an increasing proportion of inappropriate, repeat prescribing of benzodiazepines in Ireland and elsewhere, with up to 33% of patients who use these drugs doing so long-term. The typical long-term benzodiazepine user is an older, socio-economically disadvantaged patient who has been prescribed these medicines by their general practitioner (GP) and dispensed them by their community pharmacist. Misuse of benzodiazepines in nursing homes and psychiatric institutions is also of concern, with one Irish study indicating that almost half of all admissions to a psychiatric hospital were prescribed these drugs, usually despite a lack of clear clinical need. Discontinuation of benzodiazepines has proven to be of benefit, as it is followed by improvements in cognitive and psychomotor function, particularly in elderly patients. It is obvious that an inter-professional effort, focusing on the primary care setting, is required to address benzodiazepine misuse and to ensure appropriate pharmaceutical care. Pharmacists must be an integral part of this inter-professional effort, not least because they are uniquely positioned as the health professional with most frequent patient contact. There is already some supporting evidence that pharmacists' involvement in interventions to reduce benzodiazepine use can have positive effects on patient outcomes. Here, this evidence is reviewed and the potential for pharmacists to play an expanded role in ensuring the appropriate use of benzodiazepines is discussed.

Keywords: benzodiazepine; pharmaceutical care; withdrawal; tapering; pharmacist; inappropriate prescribing; sedation; dependency; cognitive function

1. Introduction

Benzodiazepine drugs were first introduced into clinical practice circa fifty years ago as anxiolytic and hypnotic agents. Despite the fact that widespread concerns surrounding their use have abounded for three decades, these drugs are still widely prescribed in most industrialized countries and diazepam is reputedly one of the most widely prescribed drugs of all time [1]. These concerns relate to their unfavourable side-effect profile, as well as their propensity for dependence and potential for abuse [2]. Moreover, the clinical effectiveness of these drugs is a question of much debate and there is growing evidence that their chronic prescription is a matter of grave concern for health professionals, legislators and, most importantly, patients [3,4].

1.1. Risk—Benefit Analysis of Chronic Benzodiazepine Use

Benzodiazepines mediate their biological activity by binding to an allosteric site on the GABA-A chloride channel, thereby enhancing GABA binding and inhibitory GABAergic neurotransmission. This results in inhibition of various other neurotransmitters within the brain, resulting in psychomotor retardation and central nervous system (CNS) depression. Benzodiazepines have a broad range of activities including anxiolytic, hypnotic/sedative, amnesic, anticonvulsant and anti-spasmodic effects, that largely reflects the distribution of different GABAergic receptor subtypes in the brain, as well as the distinct affinity of particular drugs for particular receptor subtypes. As such their therapeutic use is also broad and includes the treatment of anxiety disorders, muscle spasms, alcohol and amphetamine withdrawal, agitation, psychosis and pre-operative sedation [1]. These drugs are generally divided into short and long-acting agents, a distinction that largely reflects differences in their pharmacokinetic handling. The short-acting agents, including lorazepam and flunitrazepam, are typically used as hypnotics, while longer-acting drugs such as diazepam (Valium) and clobazam are more commonly used as anxiolytics, as anti-convulsants and in the treatment of muscle spasm.

The well-documented side-effects of long-term benzodiazepine use include cognitive impairment and memory deficits impairment in motor skills, and significant physical and psychological dependence that can precipitate a potentially fatal withdrawal syndrome, including raised blood pressure and seizures [5–8]. Attendant consequences of impaired motor performance include increased incidence of hip fractures due to falls, and road traffic accidents [9–12]. Moreover, prescribing guidelines specifically discourage their prolonged use in elderly people owing to risks of confusion, depression, dizziness and ataxia in this patient group [13,14]. Long-acting agents can be particularly problematic in the elderly, due to their age-related reduction in metabolic function [10]. Recent evidence suggests that benzodiazepines, including diazepam and lorazepam, increase the risk of pneumonia occurrence and related mortality [15]. The abuse potential of benzodiazepines is somewhat more difficult to assess but it is clear that a “black market” for these drugs does exist and that prescribed medication is frequently diverted to other users who are not consuming them under the care of a healthcare professional [16]. Benzodiazepines in overdose can induce respiratory depression and coma and they are a very significant cause of mortality, particularly in the elderly population [17,18]. A recent report in Ireland has suggested that they are a factor in 31% of drug-related deaths, and this statistic is mirrored in many countries worldwide [19].

These drawbacks to benzodiazepine use ultimately always outweigh their benefits and therefore underpin prescribing guidelines. Although benzodiazepines do show some efficacy in the short-term alleviation of anxiety, and long-term users generally perceive them to be beneficial in promoting sleep [20], meta-analyses of clinical trials generally point to a lack of efficacy [21]. It is clear that tolerance quickly develops such that any benefits they do have in the short term wear off after a few weeks of use, especially in relation to the treatment of insomnia. Thus, in general these drugs are no more effective than placebo in treating generalized anxiety disorder or insomnia in the long-term, despite these being the two most common reasons for their prescription [22]. Moreover, evidence suggests that while they may have long-term efficacy in limited patient groups including those with panic disorder and social phobia [23–25], the proportion of benzodiazepine users who fall into these diagnostic categories is very low, suggesting that the vast majority of long-term users do not derive clinical benefit from benzodiazepines [26]. Another notable clinical disadvantage of these drugs is that while tolerance develops readily to their clinical anxiolytic and hypnotic effects, it does not develop to the problematic amnesic and cognitive impairment side effects.

The benefits of benzodiazepine withdrawal have also been proven. For example, in a 3-year follow-up study, Rickels *et al.* [27] found that 73% of patients tapered off benzodiazepines were managing without anxiolytic medication 3 years after stopping these drugs compared with only 39% of patients who had reduced their use, but not stopped, the drugs and 14% of those that refused to participate in the original programme. In elderly nursing home residents, measures of memory and cognitive function improved after they were tapered off benzodiazepines [28]. In one large community-based study in which 192 long-term benzodiazepine users were recruited in 25 GP practices, patients who successfully withdrew from benzodiazepines, with tapering over 3 or 6 months, had improved performance on several psychomotor and cognitive tasks *versus* controls [29]. Economic benefits of benzodiazepine withdrawal also ensue since these drugs are prescribed frequently without clinical need or benefit, leading to a waste of resources [2,30].

1.2. Prescribing Guidelines for Benzodiazepines

Most developed countries have issued prescribing guidelines for benzodiazepines, and Ireland was quite advanced in doing so with in 2002, the Benzodiazepine Committee of the Department of Health recommending that these drugs should not be prescribed for longer than 2–4 weeks, depending on their indication, with slightly longer treatment periods permitted for anxiety relief in comparison to insomnia [31].

In the UK, the Committee on Safety of Medicines (1988) recommended that benzodiazepines be used only for the short-term (2 to 4 weeks) relief of “anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness” [32]. They also recommended that short-term use of benzodiazepines is suitable for the short-term relief of severe or disabling insomnia by itself. Subsequently they applied the same guideline for the non-benzodiazepine drug zopiclone, which is also used to treat insomnia. Very similar guidelines have been issued in Denmark and Norway [33].

Similarly, in the USA, the American Psychiatric Association Task Force on Benzodiazepine Dependency drew up a set of guidelines that urged physicians to always endeavour to use the lowest possible therapeutic doses of benzodiazepine for the briefest possible time and to only allow for long-term

maintenance of patients on benzodiazepines in rare cases where benefits outweigh the risks [34]. Typically these would include patients with very persistent severe dysphoria or anxiety secondary to another medical condition, and patients with chronic panic disorder or agoraphobia for which benzodiazepines are deemed to be drugs of choice [28].

In Australia & New Zealand, the guidelines specify that benzodiazepines should be used short-term as part of a broader treatment plan and at minimal effective doses [35]. In addition, the Royal Australian College of General Practitioners (RACGP) [36] recommends that patients being prescribed benzodiazepines are recommended to obtain all such prescriptions from the same doctor, so that the prescriber may monitor their risk of dependence [36]. Moreover, the RACGP also issues guidelines for withdrawal as well as for the prescription of these drugs, advocating switching of patients to longer-acting agents prior to the commencement of tapering and highlighting the need for patient co-operation and informed consent.

1.3. Surveys of Benzodiazepine Usage Patterns

Many surveys have been conducted internationally on benzodiazepine prescribing and usage patterns. Although direct comparisons between studies can be hampered by heterogeneity (e.g., around the definition of a long-term user), most such surveys support the notion that these drugs are in general over-prescribed without justified clinical need in many instances.

In Norway, benzodiazepine use in the primary care setting was investigated with over 3,000 prescriptions written by GPs in a 2-month period being analysed [37]. This indicated increasing dose with age, a higher proportion of prescribing to females, and a high percentage of repeat prescribing (82%), all of which point to a lack of compliance with National guidelines. A population-based study in Finland found that one third of home-based patients older than 75 years were using either benzodiazepines or related drugs chronically as sleeping aids or anxiolytics [38], while follow-up studies found that many of these users were taking these drugs on a long-term basis [14]. In the UK, benzodiazepine prescribing is reported to be falling with the Z-drugs (zolpidem, zopiclone and zaleplon) taking over, but the numbers being prescribed drugs for hypnosis are still very high and are not in alignment with guidelines issued by the UK National Institute of Clinical Excellence [39].

In Italy, trends in antidepressant and benzodiazepine use were tracked over a nine-year period and while anti-depressant use tripled, benzodiazepine use was relatively stable [40]. However, two subsequent studies in Italy both documented a high prevalence of chronic use (mean of over 2 years) without increased dosage being used to counteract tolerance [41,42]. The prevalence rate of chronic benzodiazepine use for more than 1 year was also high in Italy—specifically it was found to be 90% in 177 patients aged 60 or older with anxiety disorders [43].

In a French telephone survey of patients in 2001, the prevalence of benzodiazepine prescribing in a cross-section of community-dwelling adults was 7.5%, and factors associated with increased use of these drugs included advanced age, female gender and social disadvantage/unemployment [44]. Again, duration of usage commonly exceeds prescribing guidelines, with more than 75% of users being prescribed these drugs for more than 6 months [44]. A more recent French study suggested a higher prevalence of psychotropic medication prescribing in adults over 65 years and pointed to a large discrepancy in GPs' intentions and actual prescribing practice with regard to efforts to reduce the overuse of these drugs [45].

A ten-year follow-up population-based study from Canada found that despite increased awareness of, and warnings regarding, risks associated with long-term use of benzodiazepines, rates of potentially inappropriate prescribing had changed very little over the period 1996–2006, with 8.4% of subjects using benzodiazepines and 3.5% doing so long-term [46]. Moreover, those authors pointed out that since early use of benzodiazepines is positively correlated with subsequent chronic use, policies may need to target younger populations than those that are conventionally studied (*i.e.*, those under age 65) in order to decrease rates of long-term benzodiazepine use.

In the USA, Simon and Ludman [47] reported that 30% of 129 outpatients aged ≥ 60 with mixed diagnoses who received benzodiazepines continued its regular use for more than 2 months in primary care settings in western Washington State. In the HARP study, also in the USA (Harvard/Brown Anxiety Disorder Research Project), benzodiazepines were prescribed to 50% of all patients diagnosed with generalised anxiety disorder and up to one third of those prescribed these drugs were taking them for as long as 12 years [48]. In Japan, a large cross-sectional review of psychotropic prescriptions in *circa* 800 patients with neurotic disorders found that the proportion of subjects being prescribed benzodiazepines for anxiolysis without antidepressants increased with age [49].

There have also been several cross-country surveys of benzodiazepine use. In the ESEMeD study, psychotropic drug use across six European countries (Belgium, France, Italy, Germany, The Netherlands and Spain) was investigated. The authors found that anxiolytic medications were the most commonly used psychotropic drugs in these countries with an overall prevalence of 9.8% and concluded that these drugs were being used non-specifically for inappropriate disorders including depression [50]. Similarly, a four-country survey across France, Germany Italy and the UK found a particularly high rate of hypnotic prescribing in France (2.5%) with temazepam, flunitrazepam and nitrazepam accounting for over 40% of all hypnotic prescriptions [51]. A comparison study of benzodiazepine use in Canada and Australia, in which dispensing data was interrogated, found that usage in Canada was over twice that of Australia with a larger number of different drugs being used in Canada and a preference for longer-acting agents in Australia [52].

In Ireland, a recent report commissioned by the government found that the number of prescriptions issued for benzodiazepines increased significantly in the period 2002–2008, despite an earlier report in 2002—the goal of which was to significantly reduce inappropriate use of benzodiazepines and attendant dependence on these drugs [19,31]. Moreover, a recent ten-year follow-up study of community dwelling older adults in which inappropriate psychotropic prescribing was assessed using Beer's criteria, reported an overall prevalence rate of 6.5% for benzodiazepine use in those aged >65 years and a 27% inappropriate psychotropic prescribing rate for those over 75 years, the vast majority of which was accounted for by benzodiazepines [53]. In the institutional setting, chronic use of benzodiazepines is of particular concern in psychiatric hospitals and in residential nursing homes. One Irish study in which sequential admissions to a psychiatric hospital were monitored, indicated that 47% of patients were prescribed these drugs, usually without defined clinical need [54]. As discussed below, many of the interventions devised to reduce inappropriate benzodiazepine use have centred on institutional settings, although it is notable that benzodiazepine use in these settings is often managed by community rather than in-house pharmacists.

1.4. Epidemiology of Long-Term Benzodiazepine Use

While surveys and audits can provide useful data on the prevalence of inappropriate benzodiazepine use, they do not address the underlying causative factors for long-term use of these drugs. However, a fairly consistent finding across different countries is that old age, socioeconomic disadvantage and female gender are all associated with propensity to misuse benzodiazepines [4,13,19,22,44]. Some studies of short-term *versus* long-term users of benzodiazepines have been conducted with a view to identifying patient-related factors that predict chronic use. In the Netherlands, circa 300 patients from 32 GP practices were recruited, half of whom were short-term benzodiazepines users and half long-term users. The long-term users were more likely to be older, to live alone, to be less well educated, to have a more serious mental health profile for which they had received prior treatment, to have attended hospital consultants more frequently, and to have a lower general health status [26,55].

Moreover, any previous use of benzodiazepines, even in the short-term, appears to be a risk factor for the later development of dependence on these drugs [56]. However, it is not necessarily the case that all long-term users of benzodiazepines are dependent on these drugs. A Dutch study, which looked at chronic users in three settings and applied both DSM-III-R and ICD-10 criteria for dependence, found that 40% of GP patients, 63% of psychiatric patients and 82% of those attending self-help groups were dependent on these medications [57]. In the same study drug type, age and educational attainment were also identified as predictors of long-term use. An interesting study in The Netherlands found that prolonged benzodiazepine use was strongly associated with the initial usage pattern and recommended that pharmacists should advise about their rational use not only at the initiation of therapy, but also at the time of the first repeat prescription being presented for dispensing in order to prevent inappropriate use and dependence [58].

The attitudes of health-care professionals to the use of these drugs is also a factor that dictates their use and misuse. There is certainly no clear consensus amongst health-care professionals on this issue, and some practitioners still encourage benzodiazepine use and engage in debate as to their relative merits [59]. It has been suggested that high levels of benzodiazepine prescription may reflect either GPs' failure to consider, or inability to suggest, alternative strategies to chronic benzodiazepine use [60,61]. Surveys aimed at assessing attitudes generally find that prescribers are somewhat aware of the problems associated with long-term benzodiazepine use but that their awareness does not effectively translate into prescribing practices. In the North of England the vast majority of GPs surveyed viewed benzodiazepine use as problematic, despite its prevalence in their communities [62]. Similarly in Thailand, 45% of GPs surveyed admitted that their prescription of benzodiazepines in the previous year had been excessive [63].

In Belgium, GPs reported that while they are cautious in initiating benzodiazepines, they feel overwhelmed by their patients' psychosocial problems and believe that they are showing empathy by prescribing these drugs [64]. Likewise, in Italy, it has been suggested that chronic use is prevalent because current guidelines for benzodiazepine usage may not be realistic in the "real world of psychiatric practice" [41]. In a postal survey of GPs in Lincolnshire, which produced 84 responses, the consensus view of GPs was that Z-drugs were perceived to be more effective than benzodiazepines in terms of daytime functioning and total sleep time and were generally considered safer for older people, despite any concrete clinical evidence to support this premise [39,65]. In Spain, general practitioners who were

surveyed were found to be very knowledgeable with regard to therapeutic indications for benzodiazepines, but much less informed about the risks of dependence that accompany their prescription [66].

While there are fewer studies regarding pharmacists' attitudes and beliefs, in the Netherlands, a questionnaire was devised in order to determine the psychological factors that predict the intentions of both GPs and pharmacists regarding patient education about benzodiazepine use [67]. The authors reported that pharmacists' intention to educate about benzodiazepine use was primarily motivated by positive outcome expectations and by social norms. Interestingly, 91% of GPs in that study claimed to educate their patients when benzodiazepines were initiated, in comparison to only 47% of pharmacists. In New South Wales, Australia, pharmacists attitudes to mental illness were surveyed to assess the impact such beliefs may have on the nature of pharmaceutical care they deliver for psychotropic medication [68]. Overall, pharmacists had a high degree of knowledge of mental health-related evidence-based interventions, with improved performance in more recently trained graduates, suggesting that the requisite motivation should be there for pharmacists to ensure that benzodiazepines and other psychoactive drugs are used appropriately.

1.5. Aims of This Study

While the need for reduced benzodiazepine use and prescribing is well rehearsed, there has been very little attention paid to pharmacist-led measures that may help to address this issue. By definition, all benzodiazepine usage is associated not only with prescribing, but also with the dispensing of those prescriptions, almost exclusively by pharmacists. Therefore, as society's experts on medicines, pharmacists must accept some of the responsibility for the inappropriate use of these drugs.

Pharmacists can play a supportive role in managing the benzodiazepine withdrawal process, including monitoring and supporting patients undergoing gradual dose reduction and delivering a broader spectrum of pharmaceutical care to those patients who are placed on adjuvant medication to manage the withdrawal process. However, it is arguably the case that pharmacists should be involved proactively in optimising the use of all drugs, including benzodiazepines, and reducing their inappropriate use. Such proactive approaches may include educational initiatives, the identification of at-risk patients, evidence-based dispensing practices, policy development and inter-professional co-operation, all of which should have an ultimate aim of improving patient outcomes.

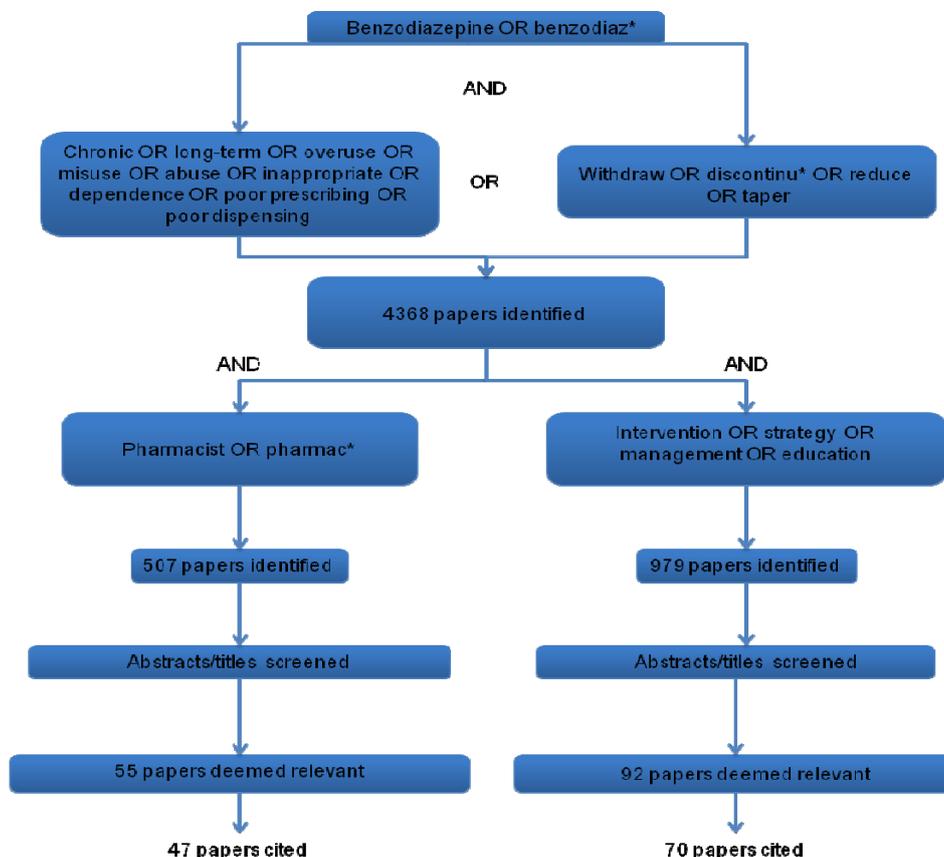
While many of those published interventions aimed at reducing benzodiazepine use do involve pharmacists, there has been very little prior consideration of the central role played by the pharmacist in this process and there have been no recent English language reviews of this topic. Here, interventional strategies for benzodiazepine reduction and discontinuation will be considered with the pharmacist's role in mind. Thus, the overall aims of this paper are to identify opportunities for the expansion of the pharmacist's role in reducing inappropriate benzodiazepine use, especially in the primary care setting, and to review current knowledge in this important area of pharmaceutical practice.

2. Experimental Section

A search of the PubMed, Embase and Cochrane Library databases was conducted 14–28 May 2013 to identify studies that evaluated pharmacist-led interventions aimed at reducing inappropriate benzodiazepine use. The search was re-run on 19 June 2013 to ensure that no relevant papers had been

published in the interim. Search terms used included: “benzodiazepine or benzodiaz*” in combination with “chronic or long-term or overuse or misuse or abuse or inappropriate or dependence or poor prescribing or poor dispensing”; or “withdraw or discontinu* or reduce or taper”; and “pharmacist or pharmac*” (Figure 1). The search was extended by manual searching of all reference lists included in articles identified in the original search. General articles about chronic benzodiazepine use and interventions that did not specifically involve pharmacists were identified in PubMed, Embase and Google scholar using the search terms: “benzodiazepine or benzodiaz*” in combination with “chronic or long-term or overuse or misuse or abuse or inappropriate or dependence” OR “withdraw or discontinu* or reduce or taper” AND “intervention or strategy or management or education”. Several current review articles on benzodiazepines were identified using the search strategy “benzodiazepine or benzodiaz*” AND “review” since 2005. Other aspects that were searched separately for supporting arguments throughout the paper included “prescribing practice” and “change”. During the review process, a paper published in July 2013 was identified as being relevant and also included. Some papers uncovered using this search strategy were not cited due to duplication or because they concentrated on other aspects that were outside the scope of this paper.

Figure 1. The main search strategy used in this study to interrogate the PubMed, Embase, Cochrane Library and Google Scholar databases. A small number of additional articles/reports around relevant topics were obtained by handsearching of reference lists and by searching for current review articles as outlined above.



A risk of bias in this study is that interventions that produce negative results are less likely to be published than those that show positive outcomes. Furthermore, with only one author involved, there was

no independent review process of articles for inclusion or exclusion. As such, the search was not conducted according to systematic review principles. The inclusion timeline for the search strategy was 1995-present, although some older papers that were uncovered manually were identified as being relevant. Exclusion criteria included articles not published in the English language and animal research. Many more general articles in which the role of the pharmacist in conducting medication reviews or medication use reviews is explored, and which may include interventions around benzodiazepines, may not have been uncovered using the search strategy. This is recognised as a limitation of this review.

3. Results and Discussion

3.1. *The Ongoing Challenge of Optimising Drug Prescribing and Drug Use*

As our armamentarium of drugs continues to increase, it is perhaps unreasonable to expect that all doctors and pharmacists can use all medicines in an evidence-based manner all of the time. However, they should, at the very least, aim to do so. Given that drugs are the number one health intervention, it is obvious that there is a large onus placed on both the prescriber and dispenser of those medicines to ensure that their patients use drugs as optimally as possible and that pharmaceutical care is delivered as a continuum. There is evidence that the improvement of professional practice in line with best practice guidelines requires an ongoing effort with constant reminders of best practice being delivered to relevant healthcare professionals [69]. In Australia, for example, a decrease in benzodiazepine prescribing was achieved in the 1990's following the issuing of revised prescribing guidelines and a public awareness campaign. However, since these campaigns ended, utilisation started to creep back up with a 21% increase in use from the years 2000–2006 observed in an elderly, socio-economically disadvantaged population [52]. Evidence from the Netherlands, where pharmacy practice is an advanced science, suggests that so-called “Dear Doctor” letters aimed at changing pharmaceutical practice are actually more effective if targeted at pharmacists rather than prescribers [70]. Those authors point out that the pharmacist has an important role to play in delivering warnings to doctors about inappropriate prescribing practices and advising them about new warnings and contraindications. Nevertheless, it is noteworthy that in terms of assessing adherence to the evidence base, there is much more emphasis placed on drug prescribing rather than dispensing or extended pharmacy practices. This applies to drugs in general as well as to benzodiazepines, which are the focus of this paper [71,72].

An interesting Irish study in which prescribing trends were assessed before and after the publication of seminal clinical trial evidence on co-prescription of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, highlighted the fact that prescribers often fail to keep up with new evidence such that it does not inform their prescribing in the way that it should [73]. There are many studies in which benzodiazepine prescribing practices have been highlighted as being less than adequate and not in concordance with published best practice guidelines. For example, in Ireland a recent survey of potentially inappropriate prescribing in a population of over 70 year-olds included long-term (> 1 month) prescription of benzodiazepines in the elderly as a poor professional practice indicator [30]. Those authors identified high rates of long-term benzodiazepine use (13% in women and 5% in men) among this population as a major contributor to the overall statistic that one third of

the Irish population in this age-group are prescribed at least one potentially inappropriate drug on the basis of European best practice criteria. Only proton pump inhibitors and non-steroidal anti-inflammatories displayed a worse prevalence of inappropriate prescribing patterns. Similarly in Sweden, the prescription of long-acting benzodiazepines to a very elderly population of nursing home residents (mean age 85) was used as a poor prescribing indicator [74]. An inappropriate prescribing rate of 16% of patients was detected, with number of prescribers per resident being positively correlated with poor prescribing performance. In a grouping of eight GP practices in Northern England, who were audited vs. their own good prescribing standards, only 31% met the acceptable standard of benzodiazepine prescription volume [75].

However, studies of poor dispensing practice are much more rare. For example, despite the fact that Olsson's and Bateman's studies (described above) involved analysis of a computerized pharmacy register/dispensing data, only poor prescribing, rather than poor dispensing or pharmaceutical care, was considered. [74,75] In one recent study, the dispensing of benzodiazepine prescriptions has been used as an endpoint for the monitoring of pharmacists' delivery of quality pharmaceutical care in Canada [76]. However, importantly since only the dispensing of long-acting flunitrazepam to the elderly was classified as contraindicated drug use, pharmacists performed reasonably well with a 4.3% inappropriate benzodiazepine dispensing rate. It would be of interest to determine all cases of dispensing outside of the agreed benzodiazepine prescribing guidelines in that jurisdiction, as this would almost certainly produce a much higher figure.

It is up to pharmacists to build this evidence base themselves and to audit their own professional practice as part of an overall strategy towards reducing inappropriate benzodiazepine use [77]. In other words, the delivery of proper pharmaceutical care requires pharmacists to act as agents of change who influence and improve both prescribing practice and overall pharmaceutical care. As discussed below and summarised in Table 1, certain pharmacist-led interventions have already been proven to be of benefit in achieving this aim and these can be directed at patients, prescribers, other healthcare professionals, policy-makers or any combination of these stakeholders.

Table 1. Summary of pharmacist-led interventions for reduction of inappropriate benzodiazepine use.

Study	Location	Pharmacist-Specific Intervention Details	Type/size & setting of study	Summary of results/Comments
Dollman <i>et al.</i> , 2005	Australia	Community pharmacists included in initial educational programme and pharmacies were used to provide information to consumers to discourage benzodiazepine use.	Before and after study (dispensing records examined in one rural area of population 20,000).	19% reduction in benzodiazepine dispensing (defined daily dose/1,000 population/day) achieved 2 years post-intervention compared with 6% nationally. Dispensing of anti-depressants increased by 33%.
Elde and Schjott, 2001	Norway	Pharmacist conducted an audit on benzodiazepine use and provided feedback and academic education to all staff.	Controlled before and after study (not randomised; 10 long-term care facilities, 5 intervention, 5 control).	Significant decrease in % of patients using long-acting benzodiazepines in intervention group (24%) vs. controls (44%). Improved drug administration practices. 5 year follow-up.

Table 1. Cont.

Study	Location	Pharmacist-Specific Intervention Details	Type/size & setting of study	Summary of results/Comments
Lerat <i>et al.</i> , 2010	France	Pharmacist and psychiatrists held monthly meetings to develop prescribing guidelines and discuss those patients receiving high-dose BDZs.	Retrospective study design. 473 prisoners (222 control and 251 intervention)	Daily dose of benzodiazepines decreased significantly from 46 mg diazepam equivalent to 34 mg in the intervention group.
McClagherty <i>et al.</i> , 1997	USA	Pharmacist conducted an audit on benzodiazepine use and provided feedback to nurses & doctors.	Quasi-experimental design across 10 nursing homes.	Percentage of patients prescribed routine benzodiazepines decreased from 4.5% to 1.6% post intervention. 3 month follow-up
Martin <i>et al.</i> , 2013	Canada	Pharmacists provided educational material directly to patients to improve knowledge of risks of benzodiazepine misuse	Before and after study with 144 participants	45% of participants had increased risk perception after the intervention. Intent to discontinue or self-taper appeared higher in the intervention group.
Midlov <i>et al.</i> , 2006	Sweden	Educational visits from pharmacist and physician focussing on “avoidance of confusion in the elderly”.	RCT design. (15 GP practices, 8 intervention and 7 control)	Significant decrease of ~25% in both total benzodiazepine prescribing and medium-long-acting benzodiazepines in intervention <i>vs.</i> control groups. One year follow-up.
Monane <i>et al.</i> , 1998	USA	Alert system established by pharmacist using computerised drug usage review system. Telephone conferences between pharmacist and geriatrician.	Population-based cohort design. 23,269 patients over 65 years from benefits manager database.	43,007 alerts triggered by system regarding suboptimal prescribing/dispensing. 24,266 alerts discussed with physician. Rate of change to a more appropriate therapeutic agent was 40% for long-acting benzodiazepines.
Roberts <i>et al.</i> , 2001	Australia	Clinical pharmacy program involving development of professional relationships, nurse education on medication issues, and individualized medication reviews.	Cluster RCT. (52 nursing homes, 13 intervention and 39 control)	Percentage of patients being prescribed benzodiazepines reduced by ~17% in intervention <i>vs.</i> control groups. Overall reduction in numbers of prescribed items per resident in intervention groups.
Schmidt <i>et al.</i> , 1998	Sweden	Monthly multidisciplinary meetings led by pharmacist, including medication review of benzodiazepine use.	RCT design. (33 nursing homes; 15 intervention, 18 control)	Improved prescribing of appropriate hypnotics (+70%) and anxiolytics (+50%) in intervention <i>versus</i> control groups. One month follow-up.

Table 1. Cont.

Study	Location	Pharmacist-Specific Intervention Details	Type/size & setting of study	Summary of results/Comments
Smith and Tett, 2010b	Australia	Community pharmacists included in educational emails about benzodiazepines. Consumers received simpler information from pharmacist when filling benzodiazepine prescriptions directing them to a website.	Controlled before and after study based on regional participation. (136 pharmacies involved; 69 intervention, 67 control)	Significant reduction in % of residents of aged care homes taking benzodiazepines after the intervention but no difference in overall benzodiazepine consumption in whole population.
Soo <i>et al.</i> , 2010	Australia	Benzodiazepine voluntary undertaking by patients enrolled with one pharmacy. Pharmaceutical care delivered.	Audit study of 129 doctors, 68 pharmacies, 606 patients.	Goals of the undertaking not currently measurable.
Towle and Adams, 2006	Scotland	Letter to repeat benzodiazepine users telling them that they have been enrolled in a step-down programme. Invited patients to attend GP for medication review. Inactivated repeat benzodiazepine prescriptions.	Sampling study (206 patients; 1 pharmacy)	At three years number of tablets prescribed down by 64% and only 23% remained on a repeat prescription for benzodiazepines. No statistical analysis performed.
Van de Steeg-van Gompel <i>et al.</i> , 2009	The Netherlands	Community pharmacists were asked to run a benzodiazepine discontinuation letter service with either written instructions alone or intensive support.	Cluster randomized controlled trial. 90 pharmacies, 47 intervention (support) 43 control (written manual)	More pharmacies in the intervention group sent discontinuation letters to long-term benzodiazepine users (70% vs. 40%), but this did not impact on the % of GPs willing to identify suitable patients to target for benzodiazepine reduction.
Westbury <i>et al.</i> , 2010	Tasmania	Community pharmacist provided audit and feedback, educational sessions and an interdisciplinary sedative review to intervention nursing homes.	Controlled trial. (25 nursing homes, 13 intervention and 12 control)	Significant reduction in the percentage of intervention home residents regularly taking benzodiazepines (31.8% to 26.9%, $p < 0.005$). No change in controls. 6-month follow-up.

3.2. Strategies for Reducing Inappropriate Benzodiazepine Use

Some of those interventions designed to decrease benzodiazepine misuse are simple ones. These include the issuing of discontinuation letters, psychotherapy or counselling, and educational strategies for both healthcare professionals and patients [35]. Pharmacotherapy approaches have also been investigated extensively, although as discussed below there is little evidence that they are any more effective than gradual tapering alone in improving cessation rates among chronic benzodiazepine users. Overall, as described below, there is good evidence that simple interventions can be effective in reducing

inappropriate benzodiazepine use, and that this process can be managed effectively in the primary care setting. Simple interventions, such as discontinuation letters, also have the obvious advantage of being cost-effective [78].

3.2.1. Role of the Pharmacist in Referring Patients to Psychological Support Services

Of these approaches, psychological interventions, including counselling and expert cognitive behavioural therapy (CBT), are least dependent on the role of the pharmacist. Baillargeon *et al.* [79] found that open-label CBT during benzodiazepine tapering attenuated rebound insomnia and prevented relapse in a group of elderly insomniacs for up to one year. Similarly, Morin and colleagues [80] reported improved success rates for benzodiazepine withdrawal when CBT and tapering were combined *versus* either intervention alone, and this was supported by polysomnographic data which provided evidence of increased stage 3 and 4 REM sleep upon withdrawal. Group CBT, which is less expensive than individual CBT may be somewhat less effective. For example, in one study in which 180 patients were randomised to benzodiazepine tapering plus or minus group CBT, both treatment groups achieved success in benzodiazepine cessation *versus* standard care, but there was no additional benefit of group CBT *versus* tapering alone [81]. There is also some debate as to whether the psychological benefits of CBT are most efficacious when they are targeted at the underlying psychiatric morbidities for which benzodiazepines were initially prescribed, rather than the withdrawal process *per se* [82]. In a recent meta-analysis, Parr *et al.* [83] included seven studies that involved psychological interventions *versus* gradual tapering alone and found that the addition of psychological intervention was superior overall to gradual tapering alone for benzodiazepine discontinuation, with a combined odds ratio of 3.38.

Referral to counselling services is arguably more appropriate for medical practitioners than for pharmacists, although for mild presentations of insomnia or anxiety it might be appropriate for pharmacists to provide patients with information on useful psychological interventions along with advice to visit their GP if their condition does not improve within a set period of time. In a recent simulated patient study in Australia, most pharmacists (96%) sold an over the counter sleep aid to “patients” presenting to their pharmacy complaining of acute onset insomnia, while the remaining 4% referred patients to a physician [84]. While the pharmacists generally scored highly on providing advice on the use of over-the-counter sleep aids, only 42% of them offered any non-pharmacological advice. Interestingly, those pharmacists with a younger age profile performed better in this task overall, suggesting that up-to-date knowledge is important in preventing inappropriate use of hypnotic agents. However, that study highlights the understandably natural tendency for pharmacists to focus on pharmacotherapy rather than consider the overall care of the patient. While it is not reasonable to expect pharmacists to have counselling or psychotherapy expertise, they should have both a willingness and competence to refer patients to other primary care professionals where it is likely to benefit their overall well being.

3.2.2. Role of the Pharmacist in Patient-Directed Educational Interventions for Reducing Benzodiazepine Use

The idea of the discontinuation letter was introduced by Cormack and colleagues in 1989 [85] and has been revised and revisited on many subsequent occasions. In essence, it may be considered a

consumer-directed educational strategy in that it comprises a short letter in which patients are advised, in a non-threatening manner, about the concerns surrounding long-term benzodiazepine use and advised to consider cutting down. Usually these letters are issued by the patient's own GP. Interestingly, several small studies, most of which have been conducted in the UK, have shown that discontinuation letters compare favourably to various other interventions in reducing benzodiazepine usage. For example, Heather *et al.* [86] found a significant benefit for both the issuing of a letter from a GP advising patients to reduce their benzodiazepine use, and a letter inviting them for a consultation along with some self-help sleep hygiene literature, but the rates of reduction were so similar in these two intervention groups that there was no significant difference between them. Similarly, Cormack *et al.* [85] found that a letter inviting patients to cut down on benzodiazepine use was just as effective in reducing utilisation as an invitation to see their GP about the issue. In a follow-up study, the same authors found that an initial discontinuation letter from the GP was just as effective as a letter supplemented with monthly advice sheets on benzodiazepine tapering [87]. In a large study in the Netherlands across 30 GP practices and including 1,700 patients, Gorgels *et al.* [88] found that while a discontinuation letter to long-term benzodiazepine users produced a significant reduction in prescriptions (24% vs. 5% for controls), that even further benefit was obtained if those letters were followed up by an invitation to attend a GP evaluation after 3 months (35% reduction in prescriptions).

There have been fewer studies in which discontinuation letters have been considered in the context of pharmacy practice. In Scotland, 369 long-term benzodiazepines users were included in a prescribing intervention study set up by a pharmacist. These patients received a letter from their pharmacist informing them that they had been enrolled in a step-down programme and inviting them to attend their GP to discuss their drug usage [89]. Three quarters of those who were invited availed of the GP appointment, and only one quarter of all patients remained on a repeat prescription for benzodiazepines at the study end. In rural south Australia, a "multistrategic" approach to benzodiazepine reduction included provision of information to consumers through community pharmacies as one of its key interventions [90]. A 19% reduction in benzodiazepine dispensing was achieved, which was 3-fold higher than the national average over the same time-period. Notably, anti-depressant dispensing increased over the same time period indicating that prescribers in that area may have adopted class switching.

In a trial involving 90 pharmacies in the Netherlands, community pharmacists were asked to run a benzodiazepine discontinuation letter service with either written instructions alone or intensive support. More pharmacies in the intensive support group sent discontinuation letters to long-term benzodiazepine users (70% vs. 40%), but this did not impact on the percentage of GPs willing to identify suitable patients to target for benzodiazepine reduction [91]. A possible confounder in this study is the poor relationship between doctors and pharmacists, which, as discussed below, is an essential component of any successful strategy for medications management in the primary care setting. The same study implied that discontinuation letters are actually more effective if delivered to patients by pharmacists rather than GPs.

In a very recent Canadian study, a written educational tool was sent to 144 benzodiazepine consumers aged ≥ 65 years recruited from community pharmacies [92]. Their knowledge and beliefs about inappropriate prescriptions were queried before and after the intervention. There was a significant increase in risk perception around benzodiazepine use after the intervention. Moreover, those patients

who used their newly acquired knowledge to identify these risks appeared significantly more likely to self-taper or discuss discontinuation with their GP.

3.2.3. Involvement of Pharmacists in Educational Interventions Directed at Healthcare Professionals

A Cochrane systematic review on educational outreach visits by pharmacists and/or physicians indicated that this approach holds promise in modifying the behaviour of health professionals, especially prescribing behaviour, although notably not all included studies showed positive benefits [93]. In the community setting, most chronic benzodiazepine users are prescribed these drugs by their GP and dispensed them by their community pharmacist. However, other professions are also involved, particularly in the institutional setting. Nurses, nurses aides, carers, psychiatrists and physiotherapists for example, may all be implicated in the mismanagement of benzodiazepines and, as described below, there are several examples of educational approaches targeted at some, or all, of these professions being of benefit in reducing inappropriate benzodiazepine use. Notably, many of these studies have been performed in the nursing home setting, reflecting the older age profile of the typical long-term benzodiazepine user. However, from the perspective of pharmaceutical care delivery, nursing homes and long-term care facilities may be considered an extension of the primary care setting in that they usually rely on community pharmacists for the procurement of drugs that are generally prescribed by a local GP.

The results of the large “RedUse” trial in Tasmania, which aimed to reduce inappropriate benzodiazepine use and involved 25 nursing homes has recently been published [94]. In that study, community pharmacists provided audit and feedback, educational sessions and an interdisciplinary sedative review to intervention nursing homes. Over a six-month period, a 20% reduction in the numbers of residents taking benzodiazepines was achieved in the intervention homes, with no change in the control settings. Moreover, 40% of residents in intervention homes were subjected to either dose reduction or cessation of benzodiazepines in this period, significantly higher than the control homes. The authors highlighted the multidisciplinary nature of the intervention, and also its co-ordination through the community pharmacy, as being key determinants of success.

Similarly, in Australia, Roberts *et al.* [95] found that the combination of education for nursing staff and a clinical pharmacist-led medication review decreased benzodiazepine use. In Sweden, multidisciplinary case conferences led by pharmacists proved effective in reducing the use of benzodiazepines, as well as other antipsychotic drugs, in the nursing home setting [96]. The successful interdisciplinary actions are in contrast to the unidisciplinary auditing approaches aimed solely at prescribing doctors who visit nursing homes, which failed to reduce prescribing rates [97]. In Norway, following on from an initial 1995 survey in which concern was expressed about the high proportion of nursing home residents being prescribed benzodiazepines [98], 5 of those nursing homes were subjected to a pharmacist-led educational intervention and followed up in another survey five years later in a before-and-after design [99]. A pharmacist, using a modified form of academic detailing, provided both written and verbal drug information to all nursing home staff members. Overall, hypnotic usage did not significantly reduce in this elderly population, but the proportion of patients taking inappropriate long-acting benzodiazepines did decrease and more appropriate usage practises (e.g., consistent timing of doses) were also observed following this pharmacist-led intervention targeted at all relevant health professionals.

3.3. Interdisciplinary Collaboration between Doctors and Pharmacists is Key to Reducing Benzodiazepine Use

As we have discussed previously, the doctor-pharmacist working relationship is of paramount importance in ensuring that patients receive proper pharmaceutical care [100]. This is particularly true in the context of benzodiazepine use, especially since withdrawal from these drugs is potentially very dangerous and must be handled and monitored carefully. Recently, a retrospective evaluation and audit of the “Benzodiazepine Voluntary Undertaking” scheme (BVU), which aimed to minimise the abuse of benzodiazepines and improve continuity of care in the Canberra region from 2004–2008, has been published [101]. That scheme, which involved 68 pharmacies, centred on a voluntary agreement between patients and their GPs to only obtain benzodiazepine prescriptions from one medical practitioner and to only have those prescriptions dispensed by one identified pharmacy. Pharmacists involved in the BVU undertook a variety of measures to ensure the validity of benzodiazepine prescriptions and on dispensing, they availed of the opportunity to re-enforce the terms and conditions of the patient’s BVU. However, notably all pharmacists involved in the programme had experienced problems with abusive behaviour by patients, who were mainly poly-addicts rather than elderly patients. They also reported that while the amount of contact between the GP and pharmacist varied significantly in administering the BVU, that they would prefer to have more doctor-pharmacist communication, and a lower administrative burden, but were positive about delivering the pharmaceutical care element of the programme. In southern Sweden, targeted visits to GP practices by a physician-pharmacist team produced significant decreases in the prescription of medium- and long-acting benzodiazepines [102]. The visits involved a group education programme on “drug treatment that may cause confusion in the elderly” delivered by both a pharmacist and a physician twice over a three-month period. Although the relevant prescribers were not alerted to subsequent auditing of their prescribing practice in this area, during a one-year follow-up a significant reduction of ~25% in long-acting and total benzodiazepine prescriptions were recorded in the intervention group.

A retrospective study of the impact of an intervention managed dually by pharmacists and clinicians to reduce benzodiazepine use in the French prison system also extolled strong co-operation between doctors and pharmacists [103]. The pharmacists played a key role in prescription review, and both pharmacists and physicians collaborated by holding monthly meetings, at which individual patients and overall prescribing guidelines were discussed. Daily doses of benzodiazepines dropped from an average of 46 mg in diazepam equivalents in the control group to 34 mg in the intervention group.

3.4. The Use of Technology in Reducing Inappropriate Benzodiazepine Use

Pharmacy is more advanced electronically than other parts of the prescribing-dispensing sequence. Although many prescriptions are still handwritten and not electronically recorded, at least 99% of all pharmacies in Ireland and other developed countries use dispensing software that automatically captures patient information and details all dispensing events. Therefore, pharmacies/pharmacists, at least on an individual basis, hold a very complete record of all benzodiazepine use. There have been many examples of electronic pharmacy records being used to determine the appropriateness of prescribing for various drug classes including benzodiazepines. In Ireland, an interrogative study of one of the

major public databases identified up to 49% of patients taking benzodiazepines and the related Z-drugs for at least 3 months, while almost 10% had been prescribed those drugs for a whole year [104]. The most recent Health Research Board report which documented benzodiazepine prescribing volumes in Ireland from 2002–2008 used dispensing/reimbursement data from the publicly funded drug schemes to produce the requisite statistics [19].

There is an obvious opportunity to use electronic dispensing data forensically to identify both rogue prescribers, and long-term users of benzodiazepines who are unlikely to benefit from these drugs. There is ample opportunity for pharmacists to initiate such strategies proactively, while bearing in mind their responsibilities regarding patient confidentiality and data protection legislation. Monane *et al.* [105] devised and implemented a computerised alert system to prompt pharmacists about inappropriate benzodiazepine use. The computer-based alerts triggered phone calls from pharmacists to geriatricians facilitating the discussion of therapeutic substitution options. Although only half of the prescribers were contactable, these telephone conferences altered prescribing in 40% of cases where long-acting benzodiazepines were highlighted as problematic. A similar approach was employed by these authors for several other drug classes that are frequently inappropriately prescribed, highlighting its general applicability. El-Aneed *et al.* [16] highlighted the potential for a computerised data network, accessible by both doctors and pharmacists, in identifying doctors engaged in the rogue prescribing of benzodiazepines, and in avoiding the release of the diversion of these drugs onto the black market. Unfortunately, many countries including Ireland do not yet have integrated drug prescribing and dispensing electronic records, but unique patient identifiers, that would facilitate this type of data integration, are likely to be introduced in the short to medium term. Interestingly, very few (<2%) Irish users of benzodiazepines admit to obtaining them from any source other than a valid prescription, although this statistic is unlikely to be entirely accurate [19].

In a recent study in Australia, Smith and Tett investigated technology as a means of providing educational information on benzodiazepines to both healthcare professionals and patients [106]. Educational material was sent to nurses and pharmacists by email bulletin on several occasions and this was followed by a consumer-focused campaign whereby pharmacists were required to give patients a bookmark each time they collected a benzodiazepine prescription, directing them to an educational website where they could obtain further information on benzodiazepine use. Although some success was achieved with this method, the study highlighted the need for pharmacists to embrace technology more enthusiastically in dealing with medication management. Fifty-four per cent of pharmacists surveyed said they would prefer to receive the educational material by mail, while only 50% of them checked their email every day! Despite this reluctant start, it seems inevitable that the information age will play an increasingly important role in ensuring the safe and effective use of drugs. As highlighted by Monane *et al.* [105] electronic alert systems prompting medications use reviews should be an integral part of any overall strategy towards using drugs, such as benzodiazepines, in an evidence-based manner.

3.5. Policy and Legal Measures

In Ireland, all benzodiazepines are classified as controlled drugs under the Misuse of Drugs legislation [107]. Flunitrazepam and temazepam are listed in Schedule 3 of this legislation, as they

were being abused more widely, while all other benzodiazepines are in the slightly less stringent Schedule 4. A similar arrangement exists in the U.K. and this means that benzodiazepines are subject to reasonably strenuous legal constraints, including a ban on repeat prescriptions such that only a 30-day supply may be issued at any one time. However, as prescription records show, prescribers and pharmacists tend to pay more attention to the administrative rather than clinical aspects of this law, such that there is little or no control over continuous prescribing on a month-by-month basis, despite the regulations banning “repeat” scripts [104]. In other words, the banning of repeat scripts for controlled drugs such as benzodiazepines may provide some control over the supply and diversion of these drugs, but does not appear to produce a patient-oriented clinical review for the need of those drugs on the writing of each individual prescription. This occurs despite the existence of a legal requirement by Irish pharmacists to deliver pharmaceutical care, including medication use review, on each dispensing occasion.

Pharmacists can only operate within the law, but they could provide an enforcement role in ensuring that benzodiazepines are used strictly within their licensing terms since chronic use in essence constitutes “off-label” prescribing. While this may require stricter benzodiazepine-specific prescribing laws as opposed to guidelines, there are relevant precedents in Irish law including the isotretinoin legislation, which are effectively managed by pharmacists. The design of the methadone protocol in Ireland provides another example of how legislation can help to avoid the abuse of drugs [108]. Arguably, the most important element of that protocol is that each patient must be enrolled with only one prescriber and one pharmacy and that a centralised database is checked each time a new patient is added to the scheme, to prevent patients engaging in “drug tourism”. The Benzodiazepine Voluntary Undertaking described above [101], in essence applied a similar model to benzodiazepine use, although it did not involve legislation *per se*.

To be truly effective, pharmacists should be pro-actively lobbying for legislative changes that have been successful elsewhere [109]. In Denmark, for example, it is illegal to write a benzodiazepine prescription exceeding four weeks, after which a full medical re-evaluation must assess their continued need [32]. It may be necessary to introduce similar legislative change, and to actually enforce such laws, in the myriad of countries in which prescribing guidelines for benzodiazepines are being ignored to the detriment of good pharmaceutical care and patient safety. In Hong Kong, a policy change including benzodiazepines as dangerous drugs, introduced in 1992, resulted in a 50% and a 10% reduction in the mean annual number of benzodiazepine prescriptions per person in the general and psychiatric populations, respectively, over the period 1991 to 1994 [110].

Not all policy changes involve legislative change, and reimbursement arrangements are also a major determinant of prescribing practice. In 2006, a restrictive drug policy was introduced by one major insurer, for nursing home residents in the USA, excluding all benzodiazepines from reimbursement. Interestingly, this policy change led to an immediate reduction of *circa* 33% in their use in patients for whom no supplemental coverage for these medicines was available [111]. However, the same authors failed to find a clinical benefit for this reduction in use, possibly reflecting increased use of Z-drug hypnotics and/or the limited outcome measure that was studied (hip fracture). Replacing one drug dependency problem with another is not likely to provide a long-term solution to inappropriate prescribing practices. Furthermore, unwarranted policies aimed at decreasing benzodiazepine use can ironically lead to detrimental effects, as seen in the 1980s in New York State when stringent benzodiazepine prescribing restrictions produced higher prescribing of several more harmful barbiturate medications [112].

Another important policy issue is whether or not pharmacists should be paid for providing extended services, including targeted interventions and more general medication use reviews, that may ultimately help reduce inappropriate prescribing of benzodiazepines and other drugs. In some of the Dutch studies, practitioners were paid a small fee per benzodiazepine discontinuation letter they issued [113]. This could provide the necessary incentive to engage pharmacists in such interventions, and may prove very cost-effective if it ultimately reduces unnecessary drug use [114]. However, cost should not be the primary motivator of policy change. Rather policy makers should always strive to consider patient outcomes foremost in the delivery of pharmaceutical care. It is also difficult in the current economic climate to negotiate an extended cost-base for pharmacists based on patient care.

3.6. Pharmacological Guidelines Surrounding Benzodiazepine Withdrawal

Benzodiazepine discontinuation in chronic users can pose a significant clinical challenge, even when they have been used at relatively low doses [115]. This aspect of benzodiazepine reduction provides an opportunity for pharmacists to deliver supportive pharmaceutical care, empathising with their patients and providing relevant counselling information on expected withdrawal symptoms [116]. They are well positioned to deliver this care since legal constraints described above generally require patients to present to the pharmacy to have benzodiazepine prescriptions filled at least monthly, and this may well be the most frequent encounter they have with any healthcare professional concerning their benzodiazepine use. Both physiological and psychological symptoms of withdrawal can be problematic for patients in the short-term and some follow-up studies suggest that over half of patients involved in a discontinuation programme undergo relapse [27]. Similar to prescribing guidelines, those physician-focused guidelines aimed at managing the patient during their withdrawal from benzodiazepines all relate a fairly consistent message, irrespective of their country of origin. Such guidelines are generally based on the consensus view, derived from relatively limited clinical evidence, that gradual withdrawal from benzodiazepines is preferable to abrupt withdrawal in terms of minimizing symptoms and thereby improving the likelihood of success (reviewed in 117). Abrupt cessation of benzodiazepines can only be recommended if a very serious side effect occurs during treatment [83].

In providing a pharmaceutical care service to their patients withdrawing from benzodiazepines, pharmacists must be aware of the current evidence base on pharmacological and therapeutic management approaches. In a Cochrane review on this topic, Denis *et al.* [117] identified eight high-quality studies/randomised controlled trials (RCT) in which the effectiveness of gradual benzodiazepine withdrawal was assessed in patients who were mono-dependent on benzodiazepines, although a meta-analysis was not possible due to heterogeneity between studies. In one of the RCTs that met their inclusion criteria, 68 patients were subjected to gradual withdrawal, by dose reduction of 25% every 4 weeks, and there were few differences in withdrawal symptoms between the groups irrespective of whether they were taking a short- or long-acting benzodiazepine [118]. In another RCT (n = 154) patient preferences and drop-out rates were used to conclude that gradual withdrawal was preferable to abrupt withdrawal in the presence or absence of hydroxyzine [119]. In another RCT (n = 31), participants were randomly assigned to either abrupt withdrawal under propranolol cover or slow withdrawal only [120]. More people in the slow withdrawal group (69%) successfully withdrew from their drugs, compared to the abrupt withdrawal group (27%). In addition, the slow withdrawal group had only mild withdrawal symptoms,

while the other group suffered more severe symptoms lasting around one month. The overall conclusion in the systematic Cochrane review was that while gradual tapering over a period of at least 10 weeks confers the greatest likelihood of success in benzodiazepine withdrawal, that there is no evidence to support the switching of patients from short-acting to long-acting benzodiazepines in preparation for the withdrawal phase, despite its pharmacological rationale [117].

There is no real consensus yet about the ideal tapering time period, although some authors suggest that to extend this unnecessarily beyond six months may be detrimental to the well-being of patients, who then tend to solely focus on this withdrawal process [2]. Furthermore, as highlighted by Denis *et al.* [117] in the aforementioned Cochrane review, there appears to be little benefit in the prescription of other drugs, including buspirone, progesterone, dothiepin, hydroxyzine or propranolol in managing withdrawal or improving abstinence rates. However, some possible benefit for the carbamazepine as an adjunct was noted, especially for those patients attempting to withdraw from benzodiazepine doses in excess of a 20mg per day diazepam equivalent [121]. A more recent meta-analysis evaluating treatment approaches for benzodiazepine discontinuation included 16 trials in which substitutive pharmacotherapies were assessed, and this review supported the notion that substitutive pharmacotherapies are not superior to gradual tapering alone in achieving successful withdrawal from benzodiazepines [83].

4. Conclusions

There has been much recent interest in pharmacists assuming an expanded role in primary care, which may include the provision of extra services such as health screening, health promotion and vaccination in the pharmacy setting. However, the most relevant area for the expansion of the pharmacist's role is in medication management, such that they ensure that medicines are being used as safely, effectively and cost-effectively as possible, in accordance with the requisite evidence base. This is, after all, a pharmacist's core area of expertise. However, the delivery of pharmaceutical care and medication management is somewhat threatened in the community pharmacy setting by economic factors. As professionals, pharmacists recognise that they have an ethical, legal and professional responsibility to provide a duty of care to their patients. But when this care involves complex therapeutic decisions and associated interventions, pharmacists should be paid for providing services over and above drug dispensing fees. Paying pharmacists to ensure drugs are only used in an evidence-based manner, while acting as an incentive, could also be self-financing, since it would arguably reduce wastage considerably.

The fact that any chronic benzodiazepine users exist at all highlights the fact that a convincing evidence base is being ignored by physicians, pharmacists and other healthcare professionals who in essence facilitate their inappropriate use. This is a waste of valuable resources and is not in patients' best interests. Moreover, since chronic benzodiazepine use is prevalent worldwide and since a recent Irish study ranked benzodiazepines third among "potentially inappropriately prescribed medicines" in an elderly population, these drugs serve as a useful model for examining the role of the pharmacist in optimising drug use. It is clear that an inter-professional approach to resolving this issue is required. Indeed several successful multidisciplinary interventions to reduce benzodiazepine use have been documented and, as outlined above, pharmacists are frequently the key driver of these interventions. Pharmacist-led interventions that reduce inappropriate benzodiazepine use include educational

interventions aimed at patients and/or other healthcare professionals, auditing and feedback studies, and the development of technology-based alert mechanisms to identify at-risk patients.

The current challenge is not in proving that these interventions work, but rather in ensuring that pharmacist-led interventions that improve the use of benzodiazepines, and ultimately benefit patients, are actually implemented and rolled out widely. The same is true of any other drugs that are used sub-optimally. Implementing changes in well-established and routine prescribing and dispensing practices is not easy, and it relies heavily on improved co-operation between doctors and pharmacists, more robust continuous professional development (CPD) arrangements, and the provision of a better policy framework. However, these are all aspects that may be driven forward by pharmacists themselves. In expanding their professional role in the future, pharmacists in Ireland must embrace a life-long commitment to CPD and research so that they establish a robust evidence base to support them in assuming more professional responsibility. They must also endeavour to drive pharmaceutical policy forward in a manner that will ensure that they always practice in an evidence-based manner. The setting of practical targets in discrete clinical areas, such as the misuse of benzodiazepines in the treatment of anxiety and insomnia, could ultimately provide a platform for community pharmacists to transform the therapeutic landscape and optimise drug use on a population-wide basis.

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Conflicts of Interest

The author declares no conflict of interest.

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