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Aust N Z J Psychiatry 2012 46: 212 originally published online 3 January 2012
DOI: 10.1177/0004867411432074

ANZJP

Australian & New Zealand Journal of Psychiatry
46(3) 212–224
DOI: 10.1177/0004867411432074

The role of alprazolam for the treatment of panic disorder in Australia

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Abstract

Objective: To investigate the potential impact of increasing prescription rates of alprazolam for the treatment of panic disorder (PD) in Australia through a review of efficacy, tolerability and adverse outcome literature.

Methods: Data were sourced by a literature search using MEDLINE, Embase, PsycINFO and a manual search of scientific journals to identify relevant articles. Clinical practice guidelines from the American Psychiatric Association, National Institute of Clinical Excellence, Royal Australian and New Zealand College of Psychiatrists and World Federation of Societies of Biological Psychiatry were sourced. Prescription data were sourced from Australian governmental sources.

Results: Alprazolam has shown efficacy for control of PD symptoms, particularly in short-term controlled clinical trials, but is no longer recommended as a first-line pharmacological treatment due to concerns about the risks of developing tolerance, dependence and abuse potential. Almost no evidence is available comparing alprazolam to current first-line pharmacological treatment. Despite this, prescription rates are increasing. A number of potential issues including use in overdose and impact on car accidents are noted.

Conclusion: Although effective for PD symptoms in clinical trials, a number of potential issues may exist with use. Consideration of its future place in PD treatment in Australia may be warranted.

Keywords

Panic disorder, alprazolam, efficacy, prescription

Introduction

Alprazolam is a high potency triazolobenzodiazepine subsidised for use through the Australian Government Pharmaceutical Benefits Scheme (PBS) in Australia for panic disorder (PD) 'where other treatments have failed or are inappropriate' (Australian Government Department of Health and Ageing, 2011). Before the selective serotonin reuptake inhibitors (SSRIs) became available (Bakker et al., 2000; Westernberg, 1996), alprazolam was a recommended first-line agent in the treatment of PD (Balestrieri et al., 1989; Ballenger, 1986; Lesser, 1991; Sheehan, 1987; Vittone and Uhde, 1985). However, concerns regarding potential long-term issues with its use (Abelson and Curtis, 1993; Fyer et al., 1987; Noyes et al., 1991; Pecknold, 1993; Pecknold et al., 1988) and availability of better tolerated alternatives led to its removal (National Institute for Health and Clinical Excellence, 2011) or relegation to second- or third-line status (American Psychiatric Association, 2009; Bandelow et al., 2008; Royal Australian and New Zealand College of Psychiatrists, 2003) in PD treatment guidelines. Despite this relegation, prescription of alprazolam continues to grow. In the decade between 1997 and 2007, PBS-subsidised prescription of alprazolam grew by 93% to 386,350 prescriptions (Australian Government Department of Health and Ageing, 2010). Over the same period, overall prescription of alprazolam (including by private prescription) grew by 99% (Australian Government Department of Health and Ageing, 2008). Similar increases in prescription

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rates have been seen in the USA, with a 71% rise over the same period (SDI/Verispan, 2008a). In that country, alprazolam is amongst the top 10 most prescribed medications, and is the most prescribed psychotropic (SDI/Verispan, 2008a,b, 2010; Belouin, 2008).

This review aims to discuss key issues related to alprazolam use for PD in Australia, with a focus on the discordance between increasing prescription rates, the evidence regarding its risk–benefit ratio and clinical practice guidelines. In particular, the review aims to discuss:

- The guideline-recommended role for alprazolam in PD
- The current prescription of alprazolam in Australia
- The relative effectiveness of alprazolam in PD compared to alternative pharmacological agents
- The tolerability issues associated with alprazolam in the short and long term
- Potential wider issues associated with alprazolam use
- The potential role of alprazolam in the future treatment of PD

Data were sourced by a literature search using MEDLINE, Embase, PsycINFO and a manual search of scientific journals to identify relevant articles using the terms 'panic' and 'alprazolam'. Clinical practice guidelines from the American Psychiatric Association (APA), National Institute of Clinical Excellence (NICE), Royal Australian and New Zealand College of Psychiatrists (RANZCP) and World Federation of Societies of Biological Psychiatry (WFSBP) were sourced. Prescription data were sourced from Australian governmental sources.

The role of alprazolam in PD treatment according to guidelines

Numerous clinical practice guidelines (American Psychiatric Association, 2009; Bandelow et al., 2008; National Institute for Health and Clinical Excellence, 2011; Royal Australian and New Zealand College of Psychiatrists, 2003) are available for management of PD. All guidelines provide recommendations on the use of specific medication classes (e.g. benzodiazepines, SSRIs) and not individual compounds in PD treatment. In this context, the role of alprazolam in PD is covered by the role of benzodiazepines generally.

All major treatment guidelines recommend the SSRIs as first-line pharmacological agents, but equally stress the role of appropriate psychological therapies (American Psychiatric Association, 2009; Bandelow et al., 2008; National Institute for Health and Clinical Excellence, 2011; Royal Australian and New Zealand College of Psychiatrists, 2003). A contributing factor to this recommendation is the high rate of comorbid depressive and substance use disorders in patients suffering from PD (Kessler et al., 2006). Data from the National Comorbidity Survey Replication in the USA demonstrated that approximately 35% of patients with PD or PD with agoraphobia suffer from comorbid major depressive disorder, and between 27% and 37% of patients suffer from comorbid substance use disorder (Kessler et al., 2006). The SSRIs (and alternate antidepressant medications) have advantages in treating comorbid depressive disorders and as a consequence of their lack of abuse liability are preferred over the benzodiazepines for patients with current or past history of substance use disorders (American Psychiatric Association, 2009).

The reported role of benzodiazepines is inconsistent across guidelines, but all guidelines suggest use beyond the short term may be inappropriate.

The NICE guidelines state: 'benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder' (National Institute for Health and Clinical Excellence, 2011). The APA guidelines cite evidence supporting earlier symptom response in patients co-administered a benzodiazepine with antidepressants. In this context they recommend 'benzodiazepines may be used along with antidepressants to help control symptoms until the antidepressant takes effect, followed by slow tapering of the benzodiazepine' (American Psychiatric Association, 2009). However, they continue to state that the short-term benefit of benzodiazepines must be balanced against 'the possibility that the patient may have difficulty tolerating the tapering and discontinuation of benzodiazepine; with ongoing use, all benzodiazepines will produce physiological dependence in most patients' (American Psychiatric Association, 2009). The WFSBP guidelines support benzodiazepines (alprazolam, clonazepam, diazepam and lorazepam) as exhibiting the same category of evidence ('A') as first-line pharmacological treatments for PD (SSRIs, venlafaxine). However, the guidelines provide similar advice to the APA guidelines, in that beyond short-term co-administration with the antidepressants the use of benzodiazepines should be restricted to treatment-resistant cases. There is an additional caveat restricting use to 'when the patient does not have a history of dependency' (Bandelow et al., 2008). The RANZCP clinical practice guidelines for PD have not been updated since 2003, but state clearly that although evidence supports the effectiveness of SSRIs, tricyclic antidepressants (TCAs) and high-potency benzodiazepines, 'benzodiazepine use is not recommended because of the high risk of creating dependency on these drugs' (Royal Australian and New Zealand College of Psychiatrists, 2003).

The current use of alprazolam in Australia

Alprazolam prescription (both PBS-subsidised and private) has grown steadily over the last decade. This appears to

coincide with an increase in overall drug utilisation. The defined daily dose (DDD) corresponds to the assumed average daily maintenance dose utilised for a drug's main indication (World Health Organization, 2011a) and is defined as 1 mg for alprazolam.A recent investigation by Hollingworth and Siskind (2010) found that on a population level, total drug utilisation of alprazolam in Australia increased from 3.88 (DDD/1000 population/day)in 2003 to 5.12 (DDD/1000 population/day) in 2007.There are many potential non-mutually exclusive reasons why prescription and utilisation of alprazolam is increasing, including:

- Increased prescription due to increasing rates of PD.
- Increased prescription due to ineffectiveness of guideline-recommended treatments.
- Increased prescription due to clinician preference, against guideline recommendations.
- Increased prescription due to patient preference or demand.
- Prescription as a co-administered medication (e.g. as needed 'PRN').
- Prescription for conditions other than PD (against PBS rules).

Increased prescription due to increasing rates of PD

Increasing utilisation of alprazolam may be secondary to an increase in the prevalence of PD. Population-based mental health surveys demonstrate that the rate of PD in Australia has increased from a 12-month prevalence of 1.3% (170,500 people) in 1997 (Australian Bureau of Statistics, 1997) to an estimated 2.6% (410,000 people) in 2007 (Australian Bureau of Statistics, 2007a). In the same period, overall prescriptions of alprazolam have increased from an estimated 308,810 in 1997 (Australian Government Department of Health and Ageing, 1997) to 616,447 in 2007 (Australian Government Department of Health and Ageing, 2008). Matching these statistics, the rate of alprazolam prescription appears to have decreased from 1.81 per patient/per year in 1997 to approximately 1.50 per patient/per year over this period. This decrease suggests increasing rates of PD may account in part for the increased number of alprazolam prescriptions. Care must, however, be taken when interpreting changes observed in these population-based surveys. The 2007 survey utilised two additional questions to determine presence of panic attacks, utilised different questions to establish the recurrent and unexpected nature of panic attacks, and did not exclude a diagnosis of PD if due to a co-occurring affective disorder (Australian Bureau of Statistics, 2007b). As a consequence, the increase in PD may be at least partially explained by methodological changes, either through providing an overestimate of the true 12-month PD prevalence in 2007 or by correcting an underestimate recorded in 1997.

Even if the change in PD prevalence is a true finding, the co-occurring increase in alprazolam prescription is surprising considering the change in clinical practice recommendations over this period. The APA's first guideline for PD was published in 1998 (American Psychiatric Association, 1998) before which alprazolam was a recommended first-line treatment. The release of the APA, NICE, RANZCP and WFSBP guidelines in the ensuing decade recommended antidepressants as first-line pharmacological treatment for PD and would be expected to have decreased the utilisation of alprazolam.

Increased prescription due to ineffectiveness of recommended treatments

Government-subsidised supply of alprazolam through the PBS is only available for the treatment of diagnosed PD where 'other treatments have failed or are inappropriate' (Australian Government Department of Health and Ageing, 2011). It is difficult to quantify how many patients with PD may fit into this category. The psychological therapies and antidepressants are generally well-tolerated interventions (although they do carry their own specific side effects), and in few patients would their use be considered inappropriate. Rates of treatment response in PD utilising antidepressants vary between studies (60–80%) (Perna et al., 2001; Pollack et al., 2007), although a significant proportion of patients (20–40%) have been shown to have continued symptoms after an initial trial of treatment (Bandelow et al., 2004; Black et al., 1993). In cases of initial treatment non-response, treatment algorithms suggest dose augmentation, psychological and physical treatments (e.g. exercise). If treatment resistance continues, switching to another first-line pharmacological agent, e.g. SSRI, serotonin and noradrenaline reuptake inhibitor (SNRI), prior to TCAs (second-line agents) is recommended. It is only after multiple failed trials that benzodiazepines (third-line agents) are recommended (Bandelow and Ruther, 2004). If treatment algorithms and guidelines are followed and trials of appropriate psychological therapies and antidepressant medications are undertaken, it would be expected that the number of patients with persisting treatment resistance would be low, although limited evidence exists in this area.

Increased prescription due to clinician preference, against guideline recommendations

Some evidence exists that use of benzodiazepines in PD may persist in preference to guideline-recommended treatments. In the Harvard Brown Anxiety Research Project, a group of 443 patients with PD had their use of psychotropic medications monitored over 10 years. In the final year of follow-up (2001) more patients were receiving benzodiazepines as a sole treatment agent (36.2%) than benzodiazepines in combination with antidepressants (21.7%) or

SSRIs alone (11.2%). This use was in clear contrast to clinical guideline recommendations (Bruce et al., 2003).

Numerous studies across medical disciplines demonstrate that despite their advantages, clinical practice guidelines are not adhered to (Hayward, 1997; Lomas et al., 1989). Cabana et al. (1999) suggest multiple barriers that can affect physician adherence to clinical guidelines, including scepticism, lack of awareness or familiarity with guidelines, a lack of outcome expectancy or self-efficacy to follow the practice guidelines and the inertia of previous practice patterns (being unable or unmotivated to change practice). In addition, barriers related to the guidelines themselves (usability, generalisability and convenience) and to patients (patient preference for a particular treatment course) were nominated as contributing factors.

Continued use of alprazolam may be influenced by prescribers' past experiences, short-term outcome expectancy and by patient preference. Alprazolam often exhibits a much faster onset of action than the antidepressants in reducing anxiety, and learning theory suggests that the shorter the duration between the treatment and the response, the more likely behaviour will be reinforced. Clinicians' desire to relieve distress as rapidly as possible may also drive preference for use over guideline-recommended treatments. In addition, alprazolam has demonstrated preferential tolerability and decreased treatment discontinuation in comparison to the TCAs in treatment trials (Schweizer et al., 1993) and in clinical audits (Cowley et al., 1997), a factor that may drive prescriber preference. The drop-out rates of SSRIs, however, appear lower than TCAs due to side effects (Bakker et al., 2002). Unfortunately direct comparative data between SSRIs and alprazolam are very limited.

Increased prescription due to patient preference or demand

Patients may prefer the use of alprazolam to the antidepressants due to the rapid rate of onset and increased tolerability. However, there is some evidence that alprazolam use is increasing faster than other benzodiazepines that exhibit similar advantages. While alprazolam use in Australia is estimated to have increased from 3.88 DDD/1000 pop/day to 5.12 DDD/1000 pop/day between 2003 and 2007, the use of other benzodiazepines including diazepam (6.16 DDD/1000 pop/day to 6.20 DDD/1000 pop/day), oxazepam (3.01 DDD/1000 pop/day to 2.48 DDD/1000 pop/day), lorazepam (0.36 DDD/1000 pop/day to 0.42 DDD/1000 pop/day) and temazepam (5.35 DDD/1000 pop/day to 4.65 DDD/1000 pop/day) demonstrated only minor increases or decreases in utilisation (Hollingworth and Siskind, 2010).

It is unclear why alprazolam use is trending differently to other benzodiazepines. One factor may be patient preference related to dependence. Alprazolam, and benzodiazepines in general, have drawn vacillating opinion over the years as to their propensity to cause dependence and/or addiction (Rosenbaum, 1993).

Addiction can be defined in a number of different ways. Some definitions imply that pleasure seeking with increasing dose is required for the syndrome.However, the more preferable definition is that of the World Health Organization (WHO) in which the addicted individual experiences a 'compulsion to take the preferred substance, has great difficulty ceasing or modifying substance use and exhibits determination to obtain (the substance) by almost any means' (World Health Organization, 2011b).

The definition of addiction does not absolutely require tolerance or physical dependence but always involves behaviours that accompany psychological dependence. These behaviours, however, may be subtle when the substance is readily available or prescribed.In this context patients who struggle to withdraw or dose reduce due to the severe anxiety associated with withdrawal from alprazolam can be considered addicted.The main contention to this argument is that the patient's failure to withdraw represents the underlying efficacy of the treatment (relapse). The difficulty in disentangling the source of anxiety (underlying or drug-induced) is a factor that complicates prescription and can be considered an undesirable quality of the pharmacotherapy.It is probable that both mechanisms may be operating simultaneously. This clinical conundrum is similar to the case of the patient who has pain but is opiate dependent.

A number of issues must be considered in attempting to quantify the impact of dependence and potential for harm, described in the following sections.

Pharmacological properties related to addiction

A combination of pharmacokinetic and pharmacodynamic properties result in a drug's addictive profile, and evidence is emerging that alprazolam may have more potent effects than other benzodiazepines upon reward pathways. Benzodiazepines, like all known addictive substances, alter mesolimbic dopaminergic pathways. Changes to evoked post-synaptic currents in the ventral tegmental area in mice can be detected after even a single dose of benzodiazepine (Tan et al., 2010). It is hypothesised that this effect is mediated by GABA-A inhibition causing secondary disinhibition of dopaminergic neurons.

While alprazolam has been associated with more severe withdrawal than other benzodiazepines, it has been more difficult to assess whether it is truly more addictive (Rush et al., 1993). There is some evidence that it produces more subjective euphoria, for example a study in patients addicted to opiates and receiving methadone revealed that they preferred alprazolam to other benzodiazepines (Iguchi et al., 1989).

Alprazolam has been found to increase striatal dopamine concentrations in rat studies, whereas lorazepam does not show this effect (Bentue-Ferrer et al., 2001), suggesting

that alprazolam may have a unique ability to interact with mesolimbic dopamine reward pathways. Behavioural reward is contingent on timing of the reward stimulus, with proximal stimuli consistently overriding distal ones. Most individuals, for example, associate the dentist with pain induction not reduction.

Alprazolam shares pharmacokinetic properties that are common to other drugs of abuse: it has a rapid onset and offset of action, high binding affinity and high potency. There are additional psychological factors worthy of consideration to help explain alprazolam addiction. Addiction to a prescription medication is generally considered more socially acceptable than illicit drug use (Hernandez and Nelson, 2010). In patients who suffer anxiety, there is a pervasive risk of the symptoms of benzodiazepine withdrawal being interpreted as the symptoms of continued affliction with panic attacks (Roy-Byrne and Hommer, 1988).

The difficulty of differentiating withdrawal from rebound or recurrence

Withdrawal from benzodiazepines includes the symptoms of 'worse anxiety, insomnia and restlessness' (Salzman, 1991). Alprazolam, due to its short half-life, also induces inter-dose rebound symptoms (rebound anxiety) in many patients, further complicating the monitoring of underlying anxiety versus a drug-induced anxiety.This cyclical rebound anxiety can lead to further dosing of alprazolam. The negative reinforcement provided by alprazolam (in the form of relief of rebound symptoms) can be a powerful mediator of psychological dependence in the patient (Juergens, 1991).

Patients taking alprazolam effectively experience at least nightly withdrawals due to its short duration of action, and the inter-dose withdrawal effects can mimic or precipitate panic.Therefore, patients can become stuck in a vicious cycle of increased alprazolam use to combat tolerance and at the same time feel more psychologically dependent to the relief provided by alprazolam. Should there be no effective alternative treatment this may be a necessary evil, but with established efficacy of the SSRIs in this patient group, the dependence potential must be regarded as a considerable adverse consequence of the use of alprazolam in the treatment of PD.

The rapidity of onset of tolerance and physical dependence

Physical dependence on benzodiazepines is due to neuroadaptation of the GABA system, resulting in under-activity when benzodiazepine dose is reduced.The onset of dependence is variable and dose related.Data from the Cross-National Collaborative Panic discontinuation study and Alprazolam SR discontinuation study show that approximately 35% of patients show withdrawal symptoms after 8 weeks taking 2 to 10 mg of alprazolam per day (Pecknold, 1993). There have also been observations of a minority of patients experiencing protracted withdrawals lasting for months after discontinuation (Ashton, 1991).

Groups at risk of dose escalation

It has been reported that dose escalation usually occurs in patients who also abuse other drugs or alcohol, and appears less likely to occur in patients without these common comorbidities. In a long-term study (mean 2.5 years) of patients with agoraphobia and panic attacks, Nagy et al. (1989) found that 70% of patients continued alprazolam (60% reduced dose, 5% same dose, 5% increased dose). Pollack et al. (1993) also found that most patients remained taking alprazolam (78%) but mean dose did not increase.It can be concluded that dose escalation may only be problematic in a minority of patients, but even without dose escalation discontinuation is difficult.

The ease or difficulty of withdrawal

Evidence indicates that alprazolam results in more severe withdrawal symptoms than other benzodiazepines.Fyer et al. (1987) found that 15 of 17 patients in a case series had recurrence or increase in panic attacks and nine had additional symptoms associated with benzodiazepine withdrawal.Thirteen of the 17 patients did not complete withdrawal within the 4 to 5 week schedule. The incidence of withdrawal reactions can be reduced by tapering more slowly, but a consistent observation is that even with slow tapering, high-potency benzodiazepines are associated with more symptomatic withdrawal (Salzman, 1991).

Long-term consequences of dependence

Of 142 patients in the long-term (mean 27.5 weeks) arm of the Cross-National Collaborative Panic discontinuation study, only 47.2% were able to discontinue alprazolam treatment.Certainly a proportion of these patients chose to stay on alprazolam due to symptom management but it is possible a proportion of the remaining 52.8% of patients suffer from adverse effects of the medication but are unable to discontinue due to withdrawal symptoms.With evidence emerging for long-term cognitive side effects and lack of comparative efficacy in comorbid depression (Birkenhäger et al., 1995) the potential harm of patients who are effectively addicted to alprazolam must be considered.

Prescription as a co-administered medication (e.g. as needed 'PRN')

A further possible explanation for increased prescription of alprazolam may relate to its use in short-term co-prescription with antidepressants, or prescription on an 'as needed' (PRN) basis. The APA (American Psychiatric Association,

2009) and RANZCP (Royal Australian and New Zealand College of Psychiatrists, 2003) guidelines suggest such usage may be appropriate, but caution this practice in the context of potential issues related to withdrawal and dependence. The practice of as needed dosing, which could be motivated by efforts to prevent dependence, is also not without its risks. The APA guidelines warns that such practice 'promotes fluctuating blood levels that may aggravate anxiety' (American Psychiatric Association, 2009) and cite evidence suggesting PRN benzodiazepine dosing is associated with worse outcomes in patients receiving cognitive-behavioural therapy (CBT) for PD (Westra et al., 2002). Rapid relief of distressing symptoms is a potent behavioural reward, which potentially drives repeated use towards later dependence.

Prescription for conditions other than PD (against PBS rules)

Although prescription of alprazolam under PBS rules is limited to PD only, it is possible that prescription is being undertaken in patients without treatment-resistant PD. There is evidence that some Australian doctors prescribe benzodiazepines outside of accepted indications (Webber, 2009), although further empirical research in this area is lacking. PBS rules are often not concordant with treatment guidelines or the evidence base, with the use of lamotrigine (Malhi et al., 2009a,b; Ng et al., 2007) in bipolar disorder being an exemplar and the motivation to help people in distress may override red tape.

The relative effectiveness of alprazolam in PD

Since its initial listing in the late 1970s, multiple short-term clinical trials have been conducted comparing alprazolam to alternative pharmacological agents (placebo, alternative benzodiazepine, TCAs and SSRIs) in the treatment of PD. The main findings are summarised below for each comparative group.

Alprazolam vs. placebo for PD

Alprazolam's superior short-term efficacy over placebo was demonstrated in numerous controlled clinical trials performed between 1980 and the early 1990s (Chouinard et al., 1982; Evans, 1981). Meta-analyses (Boyer, 1995; Cox et al., 1992) of the known controlled trials of alprazolam demonstrated clear advantage in reduction of panic symptoms.The first and second Cross-National Collaborative Panic Studies (CNCPS) (Ballenger et al., 1988; Cross-National Collaborative Panic Study SPI, 1992; Noyes et al., 1988) remain the largest randomised placebo-controlled trials of alprazolam use in PD. The first CNCPS (Ballenger et al., 1988; Klerman, 1988; Noyes et al., 1988; Pecknold et al., 1988) randomised over 500 patients from Australia, the USA and Canada with DSM-III criteria agoraphobia with panic attacks or PD into alprazolam (flexible dosing to reach 6 mg daily in 3 weeks) or placebo groups for 8 weeks. Outcome measurements assessing anxiety, global improvement, panic attacks and anticipatory anxiety episodes demonstrated a significant advantage to alprazolam over placebo at 4 weeks. However, completer analysis at 8 weeks demonstrated no significant advantage to alprazolam in frequency of panic attacks and more moderate effects in other domains (Ballenger et al., 1988). In addition, the improvement attributable to alprazolam reversed in many patients after drug withdrawal (Pecknold et al., 1988). This finding is similar to studies with other agents (SSRIs) in PD that demonstrate high relapse rates after treatment cessation (Mavissakalian and Perel, 2002; Toni et al., 2000). A major issue with this trial was patient drop-out, most notably in the placebo arm, which has led to debate over the validity of these results (Marks et al., 1989). However, given the large number of controlled trials supporting efficacy of alprazolam in controlling symptoms of PD (Andersch et al., 1991; Curtis et al., 1993) the WFSBP guidelines have attributed it with category A evidence ('full evidence from controlled studies') (Bandelow et al., 2008) for PD treatment.

Alprazolam vs. TCAs for PD

Most head-to-head trials involving alprazolam in PD have utilised the TCAs, notably imipramine (Charney et al., 1986; Cross-National Collaborative Panic Study SPI, 1992; Rizley et al., 1986) as comparator. The CNCPS-II study (Cross-National Collaborative Panic Study SPI, 1992) randomised 1168 patients from 12 study centres with a lifetime diagnosis of DSM-III criteria PD for 8 weeks into placebo, alprazolam and imipramine groups. Dosage was titrated flexibly aiming to reach 6 mg of alprazolam and 150 mg of imipramine daily by 3 weeks. Patients were assessed on multiple outcome measures including 'overall clinical efficacy and improvement', 'panic anxiety', 'phobias', 'anxiety' and 'social functioning' (Cross-National Collaborative Panic Study SPI, 1992). Alprazolam and imipramine demonstrated efficacy in most measured domains over placebo. The benefit of alprazolam appeared earlier (1–2 weeks) than imipramine (4 weeks) with both drugs exhibiting similar responses at week 8. A significant placebo response was observed in some outcomes. Similar to the CNCPS-I trial, many alprazolam patients experienced rebound anxiety and withdrawal symptoms after drug discontinuation (Abelson and Curtis, 1993; Fyer et al., 1987; Noyes et al., 1991; O'Sullivan et al., 1994; Pecknold et al., 1988), although patients assigned alprazolam exhibited less discontinuation due to side effects than those taking TCAs.

Over the longer term, there is in addition some evidence supporting alprazolam as being more efficacious than

imipramine in controlling panic symptoms (Rickels and Schweizer, 1998), although outcomes from another long-term follow-up (Andersch and Hetta, 2003) did not replicate this finding.

Alprazolam vs. alternative benzodiazepines for PD

Controlled trials in PD have compared alprazolam to the benzodiazepines diazepam (Dunner et al., 1986; Noyes et al., 1996), clonazepam (Davidson and Moroz, 1998; Herman et al., 1987; Rosenbaum et al., 1997; Tesar et al., 1987, 1991), lorazepam (Charney and Woods, 1989; Schweizer et al., 1988, 1990), etizolam (Meco et al., 1989) and adinazolam (Pyke and Greenberg, 1989).In general these trials failed to demonstrate superiority of alprazolam over alternate benzodiazepine in the management of PD symptoms or in clinical tolerability. A recent meta-analysis of controlled clinical trials found no significant advantage of alprazolam over comparator benzodiazepine (Moylan et al., 2011) across measured domains in PD treatment.

Alprazolam vs. SSRIs for PD

Multiple clinical trials and meta-analysis have found SSRIs to have equivalent efficacy but better tolerability to TCAs (Anderson, 2000; Bakker et al., 2000, 2002, 2005; Otto et al., 2001).Only one trial (Saida and Svjetlana, 2005) directly comparing alprazolam and an SSRI (sertraline) has been published to date to our knowledge. In this study, sertraline 50 mg was compared with alprazolam (1–1.5 mg/day) in a small group of randomised outpatients with PD. No difference in outcomes was found between sertraline and alprazolam in broad measures of anxiety (Hamilton Anxiety Rating Scale, HAM-A) and agoraphobia over 6 weeks. A meta-analysis comparing the efficacy of SSRIs to imipramine (150 mg/day), alprazolam (4 mg/day) and placebo demonstrated superiority for SSRIs in control of panic symptoms (Boyer, 1995), with this result less pronounced in trials with larger mean doses of alprazolam and TCAs. Another meta-analysis performed in 2005 (Mitte, 2005), however, failed to demonstrate significant differences between the efficacy of benzodiazepines (grouped), TCAs and SSRIs.

Important considerations from efficacy literature

An important consideration in the alprazolam efficacy literature is the choice of outcome measures utilised. The majority of studies involving alprazolam utilised broad measures of PD severity (e.g. HAM-A, counts of panic attack frequency, global impression scales) in assessing efficacy. Such measures lack the advantages of specific ratings scales for PD, e.g. Panic and Agoraphobia Scale (P&A) (Bandelow et al., 1998) and Panic Disorder Severity Scale (PDSS) (Shear et al., 1997) that measure multiple domains of PD symptomatology and have greater sensitivity in detecting placebo–drug differences in PD. The predominant use of broad measures versus specific PD rating scales in the alprazolam studies may not provide the most reliable evidence of its overall treatment effect in PD, specifically in domains not associated with panic attacks (e.g. quality of life) (Bandelow et al., 2007), making comparisons to newer treatments (e.g. SSRIs) assessed on these domains more difficult.

Tolerability of alprazolam in the short and long term

Short-term side effects and tolerability

Alprazolam exhibits a similar side-effect profile to other benzodiazepines (Ballenger et al., 1988; O'Sullivan et al., 1994; Verster and Volkerts, 2004). An investigation of adverse effects recorded in the CNCPS II trial (Cassano et al., 1994) demonstrated significantly increased rates of sedation (44% vs. 16%), fatigue/weakness (18% vs. 12%) and memory problems (15% vs. 9%) (Cassano et al., 1994) with alprazolam over placebo at week 4. Other reviews (Jonas and Cohon, 1993) and reports from major studies (Ballenger et al., 1988; O'Sullivan et al., 1994) also report significant side effects with alprazolam use including irritability, poor concentration, slurred speech, decreased appetite and weight loss. Alprazolam can lead to rebound insomnia, with rapid tolerance developed to short-term sleep-inducing effects (Kales et al., 1987). Most side effects were most prominent early in treatment, decreased throughout treatment courses but were maintained above placebo in long-term studies (Andersch and Hetta, 2003, Pollack et al., 1993; Rickels and Schweizer, 1998).

Rebound anxiety and withdrawal symptoms

Rebound anxiety and withdrawal symptoms are clinically significant issues with the use of alprazolam (Verster and Volkerts, 2004) and have been discussed at length previously. Rebound anxiety and inter-dose symptom return are common with discontinuation of alprazolam (Andersch et al., 1991; Fyer et al., 1987; Pecknold, 1993; Pecknold et al., 1988), and appear to occur more often than with other benzodiazepines (Wolf and Griffiths, 1991). Rebound anxiety, issues with withdrawal syndromes and physiological dependence 'appears to be greater among patients taking benzodiazepines with short-to-intermediate elimination half-lives' (Chouinard, 2004). Alprazolam demonstrates a short half-life, a high binding affinity to the GABA receptor and a rapid onset and offset of action, properties that are associated with greater risk of dependency and withdrawal (O'Brien, 2005).

Longer-term side effects

Chronic alprazolam use is associated with long-term adverse effects (Verster and Volkerts, 2004) on memory (Leufkens et al., 2007; Vermeeren et al., 1995; Verster et al., 2002), driving ability (Leufkens et al., 2007; Rapoport et al., 2009; Vermeeren et al., 1995) and psychomotor performance (Leufkens et al., 2007; Vermeeren et al., 1995). The level of memory impairment produced by benzodiazepines appears to be related to a higher relative lipid solubility and affinity at benzodiazepine receptor (Chouinard, 2004). Alprazolam exhibits both high relative lipid solubility and high binding affinity.

Wider issues with alprazolam

Abuse potential and non-clinical effects

Probably as a consequence of its high potency, rapid onset and short half-life (Chouinard, 2004; Mumford et al., 1995; Wolf and Griffiths, 1991), alprazolam has become a drug of abuse (Forrester, 2006; Substance Abuse and Mental Health Services Administration, 2010). Discussion regarding the potential for alprazolam to induce dependence is found earlier in the review. Some researchers suggest continuing use of alprazolam (Australian Bureau of Statistics, 2010; SDI/Verispan, 2010) may represent ongoing clinical management of chronic conditions rather than drug dependence (Romach et al., 1991, 1992; Sellers et al., 1993). A qualitative investigation of youth attitudes concerning alprazolam revealed use was deemed common, the drug was highly addictive, difficult to cease and medical professionals were the greatest facilitators of use (Peters et al., 2007), indicating that at least a portion of ongoing use may relate to drug dependence.

Alprazolam is a common drug in overdose incidents leading to emergency department admissions (Buukx et al., 2010; Substance Abuse and Mental Health Services Administration, 2010). Data from the US Substance Abuse and Mental Health Services Administration (SAMHSA) showed that alprazolam is the most common benzodiazepine involved in emergency overdose situations, both in isolation and mixed with alcohol and other substances (Substance Abuse and Mental Health Services Administration, 2010). These data also suggest the incidence of alprazolam events is increasing at a faster rate than other benzodiazepines, from approximately 46,000 in 2004 to 80,000 in 2008 (73% increase) (Substance Abuse and Mental Health Services Administration, 2010). This finding may relate to the fact that alprazolam is the most utilised benzodiazepine in the US population.In an Australian study of emergency department visits, the majority of alprazolam used in overdose was obtained through doctor prescription (Buukx et al., 2010). This high use of alprazolam in overdose is noteworthy, as in such situations alprazolam has demonstrated greater toxicity than other benzodiazepines with patients in one study 2.06 times more likely to require treatment in an intensive care unit than other benzodiazepines after adjusting for age, dose, gender and co-administered drugs (Isbister et al., 2004). It should be noted, however, that in overdose alprazolam (like other benzodiazepines) may be safer than other medications utilised for PD (e.g. TCAs).

The impact of benzodiazepines on driving ability is a controversial area. In a study testing driving ability of 20 health volunteers administered alprazolam 1 mg, six of the subjects demonstrated impairment to the point of unsafe driving (Verster et al., 2002). Acute administration of alprazolam 1 mg has been equated to a blood alcohol concentration of 0.15% (Verster and Volkerts, 2004), significantly higher than most country legal limits, although whether use is causally related to road traffic accidents is disputed (Barbone et al., 1998; Smink et al., 2010). Benzodiazepines are commonly found in blood samples taken from drivers involved in major trauma accidents in Australia (15.6%) (Ch'ng et al., 2007) or apprehended due to dangerous or erratic driving in Norway (46.2%) (Christophersen and Morland, 2008). Recent data from individuals involved in car accidents in Victoria (July 2009 to July 2010) found that all of those with alprazolam in their blood were responsible for the collision (Ogden et al., 2010).This data also demonstrated that alprazolam levels found in patients were well above those expected from therapeutic dosing, with the mean level 0.138 mg/L in the toxic range (Ogden et al., 2010). This probably indicates this group of patients were using alprazolam outside of normal prescribing patterns potentially indicative of an abuse pattern. Impairment of motor coordination occurs in a dose-dependent fashion and hence care should be undertaken with driving when changes or initiation of benzodiazepines has occurred.

What is the role for alprazolam in the future of PD treatment?

Alprazolam is without doubt the most investigated benzodiazepine in the treatment of PD and consideration of its place in future treatment should be made in this context. However, the available comparative evidence does not suggest that alprazolam confers an advantage over other benzodiazepines in PD treatment (Moylan et al., 2011) and it may potentially have more pronounced adverse effects owing to its high potency and short half-life. There are currently 11 different benzodiazepines in oral preparations available within Australia, with at least 28 different trade versions (Australian Government Department of Health and Ageing, 2011). Probably the best comparator benzodiazepine is clonazepam (Rosenbaum, 2004), owing to its high potency but longer half-life (Crevoisier et al., 2003), and it may potentially mitigate some of the problems associated with alprazolam use including inter-dose anxiety and strong withdrawal phenomenon (Herman et al., 1987).

Some studies have demonstrated successful discontinuation of clonazepam if achieved through a gradual taper (Moroz and Rosenbaum, 1999; Nardi et al., 2010). In addition, a randomised controlled trial investigating potential strategies for managing PD refractory to initial treatment utilised clonazepam as augmentation to sertraline (after non-response to sertraline only or secondary dose increase) and found no difference in augmentation versus institution of CBT on a variety of panic scales (Simon et al., 2009).

Inappropriate prescription of a medication is more likely to occur where prescribers have less experience or familiarity with the appropriate use of the drug and knowledge of available alternatives. Given alprazolam has only a narrowly defined supported indication under the PBS, and limited indication in the treatment of PD in clinical practice guidelines, it is possible a lack of familiarity with treatment guidelines is contributing to inappropriate use. High rates of alprazolam use and diversion were recently targeted in Tasmania through a combination of education campaigns and new restrictions on prescribing (Galloway, 2007; Hooper et al., 2009). A 12-month follow-up of this effort demonstrated a 15.4% reduction in alprazolam prescriptions over the year, in contrast to a 1.3% increase in prescriptions throughout the rest of Australia (Hooper et al., 2009). Such moves could be distributed more widely in an effort to decrease potentially inappropriate prescriptions. It is however not known to what extent alprazolam is misused. The 'total consumption model' may have validity in predicting rates of misuse in alprazolam. In this model, the proportion of individuals with excessive use (misuse) of a substance (e.g. alcohol) increases as the overall average population consumption increases (Skog and Rossow, 2006). Although classically described in alcohol (Skog and Rossow, 2006) and gambling behaviours (Hansen and Rossow, 2008), the model was recently tested in the use of prescription medicine carisoprodol in the Norwegian general population. Results suggested that the rate of excessive carisoprodol use was highly correlated with the quantity of carisoprodol dispensed (Bramness and Rossow, 2010). It is not currently known if the same association is present for use of alprazolam, but if confirmed, would suggest that increasing prescription and utilisation are potentially associated with an increased incidence of medication misuse.

Conclusion

The current place of alprazolam in treatment of PD in Australia merits renewed consideration. Further research into how alprazolam is used by patients, to what extent prescription rates reflect actual medication consumption, and into the rates of alprazolam diversion (e.g. illicit use) is required. Further, the development of best-practice strategies for managing treatment-refractory PD with subsequent integration into clinical practice guidelines would assist prescribers in managing this population of patients. Such guidelines could provide information about the relative effectiveness of less studied but widely utilised benzodiazepine alternatives (e.g. diazepam) for PD treatment and where short-acting benzodiazepines such as alprazolam or lorazepam may be most appropriate (e.g. in short-term or PRN use). This work would assist in determining what place alprazolam has in the future of Australian PD treatment.

Funding

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

Declaration of interest

SM, FG and TN declare no conflicts related to the production of this manuscript.

MB has received Grant/Research Support from Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma and Servier, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvayand Wyeth, and served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck and Servier.

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