A review of the suitability of duloxetine and venlafaxine for use in patients with depression in primary care with a focus on cardiovascular safety, suicide and mortality due to antidepressant overdose

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Abstract: Depression and anxiety disorders are among the most common disorders treated by general practitioners (GPs) in the UK. Since both disorders are associated with a significantly increased risk of suicide, including with antidepressant overdose, the safety of antidepressants in overdose is of paramount importance. Numerous updates relating to antidepressant safety have been issued by regulators in the UK which may have eroded GP confidence in antidepressants. Venlafaxine, a serotonin nor adrenaline reuptake inhibitor (SNRI) had primary care prescribing restrictions placed on it in 2004 due to concerns about cardiotoxicity and mortality in overdose. Although a review of the evidence led to a reversal of the majority of restrictions in 2006, evidence suggests GPs may still be cautious in their prescribing of venlafaxine and possibly other SNRI antidepressants for patients with depression and anxiety disorders. This paper reviews the evidence pertaining to the safety of SNRI antidepressants from a perspective of cardiovascular safety and overdose. The currently available evidence suggests a marginally higher toxicity of venlafaxine in overdose compared with another SNRI duloxetine and the selective serotonin reuptake inhibitors (SSRIs), although this may be related to differential patterns of prescribing in high-risk patients. Based on this review SNRIs have a positive risk benefit profile in the treatment of depression and generalized anxiety disorder in primary care, especially as second-line agents to SSRIs.

Keywords: cardiovascular, depression, duloxetine, mortality, primary care, suicide, venlafaxine

Introduction

In England the adult psychiatric morbidity survey of 2007 found the weekly community prevalence of a depressive episode to be 2.3% and that for generalized anxiety disorder (GAD) 4.4% [Bebbington *et al.* 2009]. It is therefore not surprising that depression and anxiety are two of the most common disorders managed by general practitioners (GPs). The vast majority of depression is treated solely in primary care with only about one in four or five patients with depression referred to secondary mental health services [NICE, 2010]. In the adult psychiatric morbidity survey 24% and 13% of people with depression

and GAD respectively had spoken with their GP in the last 2 weeks and 65% and 52% within the last year. This results in a considerable burden on GPs with a UK primary care survey finding that 7.2% of consecutive consultations were for probable depression [Ostler *et al.* 2001]. In the UK there has been a significant focus on improving treatment and services for people with depression and anxiety disorders, with the National Institute for Health and Clinical Excellence (NICE) recently updating their guidance on the management of depression [NICE, 2010] and GAD [NICE, 2011]. Much of this focus has been on increasing the availability of psychological services, but

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pharmacological therapies are still a core component of treatment for both conditions, particularly for more severe presentations or when psychological treatments have been ineffective.

The mainstay of pharmacological treatments for depression and GAD are antidepressants, and in the UK 95% of all prescriptions for antidepressants are issued by GPs [Henry, 1993; NICE, 2010]. In the UK, prescribing of antidepressants in primary care has been increasing steadily over the last decade, which has been explained mainly by an increase in the proportion of patients receiving long-term treatment [Moore *et al.* 2009]. In England during the 3 months to September 2011, over 11 million prescriptions for antidepressants were prescribed in primary care [National Health Service Business Services Authority, 2011] making them one of the most commonly prescribed classes of drugs [National Health Service Information Centre for Health and Social Care, 2010]. Selective serotonin reuptake inhibitors (SSRIs) are recommended by NICE as first-line pharmacological treatment for both depression and GAD and the dual action antidepressants serotonin and noradrenaline reuptake inhibitors (SNRIs) are among the second-line treatments [NICE, 2010; 2011]. Drug safety is one of the key considerations when prescribing in primary care and this is particularly applicable in conditions such as depression and anxiety when there is a risk of suicide by antidepressant overdose among other means and the disorders are often accompanied by other psychiatric and medical comorbidities. However, the safety of antidepressants has been called into question over the last decade. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has issued guidance on a number of safety issues, including suicidal behaviour [MHRA, 2007], discontinuation reactions [MHRA, 2004], use in pregnancy [MHRA, 2010a, 2010b], risk of fracture [MHRA, 2010c], cardiotoxicity and toxicity in overdose [MHRA, 2004, 2011] related to antidepressants. These warnings have applied to some of the most commonly prescribed antidepressants in primary care. For example, the most recent guidance regarding QT prolongation [MHRA, 2011] relates specifically to citalopram, the most commonly prescribed SSRI in the UK [National Health Service Business Services Authority, 2011], and its related compound escitalopram. These recommendations are potentially alarming for GPs and patients and may undermine the confidence in antidepressants in general. However,

it is important that the safety data relating to antidepressants are fully understood in the context of treating depression when, for many patients, several different antidepressants have been prescribed before an effective treatment is found. One important group of antidepressants for which there have been safety concerns in the past is the SNRIs. There is evidence to suggest that the confidence of GPs in the safety of the SNRI venlafaxine may have been eroded following the MHRA urgent safety restriction (USR) issued in 2004 [MHRA, 2004] after which prescribing rates diminished over the next year [McAllister-Williams *et al.* 2006]. Venlafaxine has been licensed for the treatment of depression in the UK since 1994 and had been increasingly prescribed by GPs and specialists as a second-line treatment for depression. The USR related to potential toxicity in overdose and it restricted the initiation of venlafaxine to mental health specialists and gave new contraindications in patients with heart disease. In 2006, after a reexamination of the safety evidence and taking into account new epidemiological data, the MHRA released updated guidance on the prescribing of venlafaxine [MHRA, 2006]. This new guidance removed the recommendation for specialist initiation of venlafaxine along with some of the contraindications, and requirement for baseline electrocardiogram (ECG) monitoring, again allowing its initiation by GPs in primary care. Despite this change of guidance in 2006, prescribing of venlafaxine in primary care has since remained static [Ilyas and Moncrieff, 2012], and against a background of increasing antidepressant use, it may be conjectured that GPs are still wary of prescribing venlafaxine in primary care. In 2005 a second SNRI, duloxetine, was licensed for the treatment of depression. We speculate that many GPs may take the view that, as an SNRI, this may also carry a higher risk of cardiotoxicity or other toxicity than other antidepressants.

This paper aims to review the data examining mortality associated with overdose of venlafaxine and duloxetine, including the data examining suicidality and cardiovascular safety. Based on this evidence, recommendations can then be made as to their suitability for use in primary care from a perspective of these major safety issues. The review will take the following structure:

- (1) Mortality due to overdose of venlafaxine and duloxetine. The evidence of how these data are synthesized and analyzed using the

fatal toxicity index (FTI) will be reviewed. This will be followed by a review of deaths from overdose using case series which are easy to understand and give further information on the safety of antidepressants.

- (2) A brief review of cardiovascular safety of the SNRIs will be presented.

Mortality due to overdose of venlafaxine and duloxetine

Measuring overdose mortality for antidepressants is relatively straightforward in the UK, but interpreting the data is difficult due to a number of factors. The simplest way of assessing overdose mortality is to count the deaths of those who have overdosed on antidepressants [available from the Office of National Statistics (ONS) who are informed via the coroners]. The number of deaths is then divided by the number of prescriptions dispensed for each antidepressant (which in England and Wales is provided by the Department of Health) to give a FTI, which is usually quoted as the number of deaths per million prescriptions dispensed [Henry, 1989]. Several analyses using a FTI calculated by this method have been published, such as those by the ONS [Morgan *et al.* 2004] and Buckley and McManus [Buckley and

McManus, 2002]. The results of these analyses are consistent with each other. The ONS data give a FTI of 43 deaths per million prescriptions for tricyclic antidepressants (TCAs), 4.3 for SSRIs and 17.6 for venlafaxine. Buckley and McManus found a FTI of 34.8 for TCAs, 1.6 for serotonergic drugs and 13.2 for venlafaxine [Buckley and McManus, 2002]. It was the ONS data, with a FTI for venlafaxine being four times that for the SSRIs, which was one of the concerns of the MHRA when the USR on venlafaxine was imposed in 2004. The analysis above, however, is simplistic. There is more to a FTI than the direct toxicity of the drug, and other considerations such as patient factors (e.g. severity of depression, history of self harm, other drugs involved in overdose) and even whether the antidepressant might itself increase suicidality can affect the FTI. These factors are shown in Figure 1.

Additionally other factors may contribute to potential bias in this type of data. For example, the indication for the antidepressant dispensing data is not recorded and therefore it is likely some patients may have been taking the antidepressant for conditions other than depression, which may have differing inherent risks of suicide and potential for drug overdose. For example, it was found

Figure 1. Patient and possible drug factors associated with suicide attempts and fatal antidepressant overdose in depression.

that 30% of antidepressants prescribed from a sample of 151 general practices in the UK were not prescribed for depression [Lawrenson *et al.* 2000]. In addition, coroners report antidepressant information voluntarily and only if they consider the antidepressant contributed to the cause of death [Morgan *et al.* 2004].

In order to better understand the FTI the following will be reviewed in turn:

- Patient factors (e.g. severity of disease and multiple concurrent medication at overdose).
- Drug factors (e.g. emergence of suicidal thoughts and inherent toxicity).

Patient factors

Most GPs will be aware that the initial antidepressant treatment of depression is with an SSRI, in line with NICE guidelines. Only patients who have a poor response, fail to reach full remission or have more severe depression may go on to receive another drug such as venlafaxine or, more recently, duloxetine. As might be anticipated, the patients who were treated with venlafaxine in the ONS data were found to have a higher burden of suicide risk factors than those prescribed SSRIs [Mines *et al.* 2005]. To try to compensate for the inherent risk factors using data from the UK General Practice Research Database (UKGPRD), Rubino and colleagues adjusted the hazard ratios for venlafaxine *versus* fluoxetine, citalopram and dothiepin (dosulepin) using proxies for severity of depression such as previous suicide attempts [Rubino *et al.* 2007]. Once these confounders had been adjusted for, the hazard ratios were substantially reduced [from 2.85, 95% confidence interval (CI) 1.37–5.94 to 1.63, 95% CI 0.74–3.59 for venlafaxine *versus* fluoxetine]. However one can only adjust for those factors that can be measured and major risk factors such as hopelessness, impulsivity, abuse, unemployment and social isolation were not measured and thus not adjusted for, meaning further confounders may still have been present in the data. Further evidence for the channelling of venlafaxine use towards patients with a higher risk of suicidal behaviour has been published using data from three primary care trusts (PCTs) in the UK [Bergen *et al.* 2010] and in an Australian study [Chan *et al.* 2010]. The MHRA has also concluded that the increased FTI is at least partially contributable to these patient factors [MHRA, 2006].

Drug factors

Drug factors can be divided into two main considerations: those involving drug-induced emergence of suicidal thoughts and behaviours, and the toxicity of individual drugs.

Emergence of suicidal thoughts

There is evidence of a small increase in suicidal behaviour in the first month after starting an antidepressant [Jick *et al.* 2004]. A recent review for the World Psychiatric Association has concluded that antidepressants carry a small risk of inducing suicidal ideation and behaviours in people under 25 years, although this risk reduces in those aged between 30 and 40 years [Moller *et al.* 2008]. There are data available on the emergence of suicidal thoughts and behaviours specific to duloxetine and venlafaxine use. Acharya and colleagues compared incidence of suicide-related events with duloxetine *versus* placebo in controlled trials, using Mantel–Haenszel incidence difference methods [Acharya *et al.* 2006]. They found no evidence of increased risks of suicidal behaviours or ideations during treatment with duloxetine compared with placebo in patients with major depressive disorder. Enstuaah and colleagues found in an 8-week study that fewer patients on venlafaxine than on SSRIs developed emergent suicidal thoughts, as shown in Figure 2 [Enstuaah *et al.* 2001]. In a recent person-level analysis of all sponsor-conducted randomized controlled trials of fluoxetine and venlafaxine, both treatments were found to decrease suicidal thoughts and behaviours compared with placebo in adult patients and older patients, although no difference was found in young patients [Gibbons *et al.* 2012]. This was mediated through decreases in depressive symptoms through treatment. The data therefore do not support an association of either duloxetine or venlafaxine with increased suicidal ideation or behaviours as a mechanism for increasing the frequency of poisonings with these agents. However, as suicidal thoughts and behaviours may still occur in individuals we would still recommend that patients who are started on an antidepressant should be monitored for the emergence of suicidal thoughts in line with good medical practice and the summary of product characteristics.

Inherent toxicity of an antidepressant in overdose

One way of assessing the inherent toxicity of a drug in overdose is to calculate case fatality rates. This method compares the rate of death from

Figure 2. Emergence of suicidal ideation in adults during treatment for depression with selective serotonin reuptake inhibitors (SSRIs), venlafaxine and placebo [Entsuah *et al.* 2001].

self-poisoning with the rate of non-fatal self-poisoning; that is, the proportion of people who die from overdose of a particular agent [Rose and Unis, 2000]. In a recent study case fatality indices were calculated for venlafaxine, TCAs and SSRIs using mortality rates and self-poisoning rates from three centres in the UK [Hawton *et al.* 2010]. Relative toxicity indices were calculated by standardizing the rate ratios to amitriptyline. The case fatality (mortality to self-poisoning ratio) for venlafaxine was found to be 2.5 (95% CI 2.0–3.1), for SSRIs 0.5 (95% CI 0.4–0.7) and for TCAs 13.8 (95% CI 13.0–14.7). The relative toxicity index to amitriptyline was reported as 0.29 for venlafaxine, 0.06 for SSRIs and 1.6 for all TCAs. Therefore, the case fatality rate for venlafaxine was found to be substantially lower than that for TCAs but still greater than that for SSRI antidepressants. However, the authors listed several possible limitations of these data which may have inflated the case fatality rates for venlafaxine. First, nonfatal self-poisonings not presenting to the hospitals could not be accounted for and therefore case fatality rates may be overestimated, although this probably applies equally to all drugs in the study. In addition, size of overdose was not considered and the indication for which the antidepressant was prescribed was not taken into account. This may affect case fatality rates if some drugs are used more frequently for conditions for which lower doses are often prescribed and overdoses may therefore be smaller. Venlafaxine has been previously demonstrated to be preferentially

prescribed to patients with longer-term psychiatric disorders and a history of self-harm [Bergen *et al.* 2010; Chan *et al.* 2010; Mines *et al.* 2005] and therefore it is conceivable that this fact may increase the case fatality rate for venlafaxine in this particular study relative to SSRIs if larger overdoses are taken. However, it should be noted that there is currently no direct evidence that patients take larger venlafaxine quantities. In addition, data from the Edinburgh Poisons Unit indicate that admissions due to citalopram, mirtazapine or venlafaxine overdose involved around 15–16 times the defined daily dose for all three agents [Waring *et al.* 2010].

A US study has used a similar method. A hazard index was calculated for each antidepressant using US poison control data (number of major or fatal outcomes per 1000 reported antidepressant ingestions) [White *et al.* 2008]. There were 5510 overdoses for which venlafaxine alone was ingested but only 12 (0.22%) were fatal and cardiac conduction disturbances were seen in only 2% of all cases. For duloxetine the data were more limited, with just 36 overdoses and no fatalities. The hazard indices were 27 for venlafaxine, 0 for duloxetine, 27 for citalopram, 22 for fluvoxamine and 6 or less for the other SSRIs. Since no data were available on indication for which the drugs were prescribed and there are likely to be other non-fatal overdoses not reported to US Poison Centres, then the same limitations as in the data reported by Hawton and colleagues apply [Hawton *et al.* 2010].

Table 1. Case fatality rates from overdose for selective serotonin reuptake inhibitors and venlafaxine from the Adverse Drug Reactions Online Data Tracking database [MHRA, 2012].

Drug	Citalopram	Paroxetine	Venlafaxine	Duloxetine	Sertraline	Fluoxetine
Number of reports with a fatal outcome with overdose	16	13	17	1	5	8
Total number of overdose reports	133	236	160	24	52	104
Case fatality rate for overdose	12.0	5.5	9.4	4.2	9.6	7.7
Data compiled from drug analysis prints of single active constituent overdoses and associated fatalities. Case fatality rate for overdose calculated by dividing number of fatal overdose reports by total number of overdose reports.						

In the UK, case fatality rates can also be calculated by examining the overdose reports from the Adverse Drug Reactions Online Data Tracking (ADROIT) database at the MHRA. Case fatality rates with overdose calculated from these data are approximately the same for venlafaxine as with the other SSRIs; see Table 1 [MHRA, 2012]. As outcomes of drug overdose are not systematically collected (although once received by either a company or the MHRA they will be formally processed and reported) the information obtained from this type of analysis, although useful in helping to identify possible safety issues with medicines, has the same obvious limitations (such as under reporting) as the previous datasets and therefore cannot be used alone to base conclusions on the safety and risks of medicines.

Thus as demonstrated above the FTI is confounded by many factors and is not a reliable way of estimating relative toxicity of antidepressants. When the confounders are adjusted for, venlafaxine appears to have similar or only slightly elevated toxicity compared with the SSRIs. The fact that the FTI is an unreliable estimate for toxicity is also demonstrated by the findings with nortriptyline, which was found to have a FTI ranging from 5.5 [Buckley and McManus, 2002] to 53.65 [Henry and Antao, 1992]. This may mean it is one of the least or one of the most toxic antidepressant agents available. The large range of FTIs reported by different authors confirms that confounders can have a large effect, as the inherent toxicity of nortriptyline would not change over time.

Case series

Observational data from clinical use regarding overdose mortality have been published as

individual case reports and case series. As case series can only include reported overdoses and outcomes they cannot tell us about relative risks between antidepressants but they are still informative as to the specific risks and outcomes associated with individual antidepressants.

Venlafaxine. The largest single drug series for venlafaxine is reported by the National Poisons Information Service in London [Colbridge and Volans, 1999] who followed up 632 patients who overdosed on venlafaxine. The main finding is that there were no deaths. Two cases of serious cardiotoxicity were reported, but one was associated with concomitant chlorpromazine and the other with thioridazine. In another large case series of 235 patients admitted to the Edinburgh Royal Infirmary following venlafaxine overdose, no deaths were reported, although a dose-dependent relationship between venlafaxine ingestion, tachycardia and corrected QT interval (QTc) prolongation was found and arrhythmias were documented in three patients [Howell *et al.* 2007]. Prolongation of the QT interval is associated with an increased risk of the potentially lethal cardiac arrhythmia, torsades de pointes, a risk that increases with the use of QT prolonging drugs [Anderson *et al.* 2002]. No cases of torsades de pointes were reported in this study and to the authors' knowledge no cases have been published in the literature, although two cases have been reported on the ADROIT database [MHRA, 2012] neither of which were fatal. The analysis by Howell and colleagues used Bazett's formula to calculate the QTc for heart rate. This is reported to overcorrect at higher heart rates [Desai *et al.* 2003] and, as venlafaxine is associated with tachycardia in overdose, this may have influenced the findings in this study. Further case series of 96

cases of venlafaxine overdose [Kelly *et al.* 2004] and 51 cases of venlafaxine overdose [Whyte *et al.* 2003] also did not report any deaths on venlafaxine. The data reported by Whyte and colleagues have now been expanded, and venlafaxine overdoses for which ECGs were recorded were available for 273 patients on 369 occasions [Isbister, 2009]. No deaths were reported and venlafaxine was only found to cause minor abnormalities in the QT and QRS interval, unlikely to be associated with major arrhythmias except possibly with large doses.

There are some data associating large overdoses of venlafaxine with cardiotoxicity [Bosse *et al.* 2008; Hojer *et al.* 2008]. In a retrospective cohort study of 36 cases of venlafaxine self-poisoning and 44 randomly selected SSRI self-poisoning cases admitted to an emergency department in Australia, one death was reported in the venlafaxine group [Chan *et al.* 2010]. This patient had ingested 12,600 mg of venlafaxine XR with propranolol, alcohol and amphetamine. No deaths were reported in the SSRI group. No clinically relevant changes in QT interval were noted. In this study venlafaxine was found to be prescribed preferentially in patients at a higher risk of serious suicide attempt.

Duloxetine. There are far fewer published cases on duloxetine overdoses. Two individual reports of overdoses on duloxetine have been reported [Kruithof *et al.* 2011; Menchetti *et al.* 2009]. Neither case was fatal. In the first report, cardiovascular alterations with hypotension, sinus bradycardia and possibly slightly prolonged QTc interval were found, and in the second, sinus tachycardia and normal QTc interval were reported.

The case series above can be contrasted with a case series of TCA overdoses published by Serafimovski in which 68 cases of TCA overdoses were followed and resulted in 57 (83%) patients having ECG abnormalities and 8 (12%) died [Serafimovski, 1975].

Cardiovascular safety

Cardiovascular safety in relation to overdose has been alluded to above, but here we will briefly review the preclinical, clinical and post-marketing cardiotoxicity data on venlafaxine and duloxetine.

Preclinical data

Of interest is whether duloxetine or venlafaxine have activity at sodium or potassium ion channels, which are the main cause of arrhythmias. Two studies in animals have shown that venlafaxine can inhibit cardiac ion channels [Fossa *et al.* 2007; Khalifa *et al.* 1999], but the concentrations of venlafaxine associated with inhibition were much greater than those seen in humans taking therapeutic doses so these are difficult to interpret. Preclinical data have demonstrated that duloxetine has no adverse effect on human cardiac sodium and potassium channels [Detke *et al.* 2005]. As there is now a wealth of clinical data for both duloxetine and venlafaxine, there is little point in dwelling on preclinical data which are of more use when a drug is under development.

Clinical trial data. A large review of the duloxetine clinical trial database which included 8504 patients on duloxetine has been published [Wernicke *et al.* 2007]. The review concluded that the use of duloxetine did not appear to be associated with significant cardiovascular risk in patients with conditions for which the drug has been approved or studied. In particular, there was nothing of concern regarding QTc interval, and this is reflected in the duloxetine summary of product characteristics (SPC) (available from www.emc.medicines.org.uk) which states 'The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients'.

In a review of the venlafaxine clinical trial database by Rudolph and colleagues, of 2897 patients who took venlafaxine, there were no serious arrhythmias or significant increase in QTc interval [Rudolph and Derivan, 1996].

Postmarketing data. A large nested case control study has also been performed to assess whether venlafaxine is associated with an increased risk of sudden cardiac death or near death compared with other antidepressants [Martinez *et al.* 2010]. This study using the UKGPRD followed 207,384 new users of venlafaxine and other antidepressants with a diagnosis of depression or anxiety for an average of 3.3 years. There were 568 cases of sudden cardiac death or near death, which were matched to 14,812 controls. The adjusted odds ratio (OR) of sudden cardiac death or near death associated with venlafaxine use was 0.66 (95% CI 0.38–1.14) relative to fluoxetine use, whereas

compared with citalopram it was 0.89 (95% CI 0.50–1.60) and with dosulepin 0.83 (95% CI 0.46–1.52). In addition, no evidence was found that venlafaxine use was associated with a higher risk of out-of-hospital haemodynamically significant acute ventricular tachyarrhythmia compared with the other antidepressants. It was therefore concluded that venlafaxine was not associated with an excess risk of cardiac death or near death compared with fluoxetine, citalopram or dosulepin in patients with depression or anxiety.

A nationwide study performed in Denmark examining the association of antidepressant use and out-of-hospital cardiac arrest (OHCA) has recently been published [Weeke *et al.* 2012]. All patients in Denmark who experienced an OHCA between 2001 and 2007 were identified (19,110 in total) and associations between specific antidepressants and OHCA examined with conditional logistic regression in case–time–control models. A total of 2913 patients were receiving antidepressants at the time of the OHCA. TCAs (OR 1.69, 95% CI 1.14–2.50) and SSRIs (OR 1.21, 95% CI 1.00–1.47) were both associated with comparable increases in risk of OHCA. No association was found for SNRIs/noradrenergic and specific serotonergic antidepressants (NaSSAs) (OR 1.06, 95% CI 0.81–1.39). Citalopram (OR 1.29, 95% CI 1.02–1.63) and nortriptyline (OR 5.14, 95% CI 2.17–12.2) had the strongest associations. Venlafaxine had the lowest OR of 0.68 (95% CI 0.38–1.22) from 177 identified cases of OHCA and hence no evidence was found that venlafaxine increased the risk of OHCA. A review of 37 patients with depression taking high therapeutic doses of venlafaxine (mean dose 346.15 mg/day) did not reveal any clinically significant change in QTc intervals [Mbaya *et al.* 2007]. However, there is a case report of significant QTc prolongation associated with venlafaxine 150 mg/day in an older lady with depression who had a QTc interval of 582 ms which reduced to 430 ms several days after discontinuing venlafaxine [Letsas *et al.* 2006].

Other cardiovascular-related adverse events

Another area of potential concern for SNRIs is well recognized and relates to the potential to increase pulse and blood pressure because of inhibition of reuptake of noradrenaline. These are covered under the SPCs for duloxetine and venlafaxine (both available from <http://www.emc.medicines.org.uk>). The SPC for duloxetine gives a warning that blood

pressure monitoring is recommended in patients with known hypertension or other cardiac disease. It also states that duloxetine should be used with caution in patients whose conditions could be compromised by an increase in heart rate or blood pressure. The SPC for venlafaxine (Efexor XL, Pfizer Ireland Pharmaceuticals, County Kildare, Republic of Ireland) is slightly different in that it recommends all patients should be screened for hypertension prior to initiation and all patients should have their blood pressure monitored. Similar to duloxetine, there is a warning for patients who might be compromised by an increase in heart rate.

Conclusion

There is now a substantial amount of clinical information on both duloxetine and venlafaxine taken at therapeutic doses and in overdose. FTI data are confounded by a number of variables, in particular differential antidepressant prescribing in patients with different baseline risks of taking antidepressant overdose. This and other confounders must be considered when interpreting FTI data as without adjustment the data prove unreliable. It must be remembered, however, that many confounders are unknown or unrecorded and therefore cannot be adjusted for. Case fatality indices suggest a slightly higher toxicity of venlafaxine than that of duloxetine or SSRIs, although venlafaxine users may have taken larger overdoses. Further studies would be required to investigate this possibility. In addition, a large nested case–control study and clinical data do not currently suggest that venlafaxine is significantly more toxic than first-line SSRIs or that it is associated with increased rates of attempted suicide, successful or otherwise. Duloxetine data are more limited but demonstrate no significant safety issues relating to suicidality or mortality from overdose compared with SSRIs. Considering as few as one-third of patients treated with SSRIs achieve full remission from their symptoms [Trivedi *et al.* 2006] there is a clinical need for alternative antidepressants. Switching to another antidepressant class after SSRI treatment failure may be a more effective strategy than within class switching [Papakostas *et al.* 2008] and data specifically support the safety and efficacy of switching SSRI treatment failures to SNRIs, such as duloxetine [Perahia *et al.* 2008, 2009; Romera *et al.* 2012]. Based on this review of the safety data from the SNRIs duloxetine and venlafaxine and the evidence of their efficacy in depression and GAD [Allgulander *et al.* 2008; Smith *et al.* 2002; Thase *et al.* 2007], both drugs

appear to have a positive benefit risk profile. This evidence suggests both duloxetine and venlafaxine are appropriate for use in primary care, especially as a second-line option following an SSRI.

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Conflict of interest statement

ALS and AB are employees of Eli Lilly and Company who manufacture and market duloxetine, an SNRI antidepressant.

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