The psychoactive effects of antidepressants and their association with suicidality.

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The psychoactive effects of antidepressants and their association with suicidality.

Abstract

Although antidepressants are known to produce some adverse mental effects, their full range of psychoactive effects has not been systematically described. It has been suggested that some antidepressants are associated with increased suicidal thoughts and actions, but the issue remains controversial, and the mechanism of association, if any, is unclear. In the current study we examined descriptions of the major psychoactive effects experienced by users of two commonly used antidepressants, fluoxetine and venlafaxine, as reported on a **patient-oriented web site**. We categorised responses into common psychoactive effects and explored associations among those effects, including reported increases in suicidal ideation. In the 468 descriptions we examined, the most commonly reported effects of both drugs were sedation, impaired cognition, reduced libido, emotional blunting, activation (feelings of arousal, insomnia and agitation) and emotional instability. Feelings of euphoria and relaxation were not common. Emotional blunting was associated with cognitive impairment, reduced libido and sedation. Emotional instability, which included the **reported side effects** of increased anxiety, anger, aggression and mood swings, was related to activation effects and was more commonly reported by younger respondents. Increased suicidal thoughts were rare but were associated with both types of emotional effect. The effects identified are consistent with other data, and suggest that some antidepressants may induce emotional effects that are experienced as unpleasant, may impact on the symptoms of mental disorders, and may account for the suggested occurrence of increased suicidal impulses in some users.

Key words

Antidepressants; selective serotonin reuptake inhibitors; adverse effects of antidepressants; fluoxetine; venlafaxine; drug-induced suicidal thoughts; drug-induced emotional effects

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Introduction

Antidepressants are known to produce a number of adverse mental effects [1], but their full range of psychoactive effects has not been systematically described. Studies of Selective Serotonin Reuptake Inhibitors (SSRIs) suggest they can produce sedation [2], "activation" effects, including agitation, insomnia and "akathisia" [3], and emotional blunting and apathy have been reported [1,4,5]. The relation between these effects **such as whether they occur singly, or together as a global state or 'syndrome'**, has not been clarified, however. The effects of other new antidepressants are even less well known. There is also continuing controversy about whether SSRIs can induce suicidal feelings in some people **or age groups**, and the mechanism of this possible effect is not understood [6,7]. There have been suggestions that suicidal thoughts and aggressive behaviour may be linked to the activating effects or akathisia produced by SSRIs, but this has not been confirmed [6,8]. Clarifying the sort of subjective state that is induced by taking antidepressant drugs may help to explain their relation to these behaviours, and is also important in order to understand how they might impact on depression, and other mental symptoms.

The limitations of current post marketing surveillance systems have lead some authors to suggest that data from patient-oriented websites may contribute to identifying adverse drug-induced effects [9]. Rising levels of internet access also mean that internet users are likely to be increasingly representative of the general population, and there is increasing interest in the internet as a forum for communication about mental health problems [10,11]. We examined data on antidepressants reported on an internet database, askapatient.com, designed for

patients to record experiences and side effects of all sorts of medications. The website was set up independently by a former librarian and it was self-funded for many years, although it now receives some income from advertisements placed on a few pages (personal communication, January, 2010).

We **analysed descriptions** relating to two modern antidepressants, fluoxetine, and venlafaxine, **which we chose because they are well known and widely used. We hypothesised that because they have slightly different pharmacological profiles, their psychoactive effects might differ somewhat.** We were also interested in exploring associations between the different types of effect reported, **to see if there is a global drug-induced state that can be identified and to explore relations with suicidality.** We defined a psychoactive effect as any effect that is primarily expressed as an alteration of normal mental processes, emotions or behaviour. For the current analysis, we excluded effects that were reported to arise during drug withdrawal. Although we were principally interested in the mental effects the drugs induced, we also recorded physical effects because the mental and physical effects of drugs are intertwined and many effects, such as sedation, have a physical and mental component. However, in this paper we focus on psychoactive or mental effects, and only report physical effects as they relate to these effects.

Materials and Methods

The website

On the www.askapatient.com website, people can record comments about a range of medicines which they are taking or have taken, including many drugs used in psychiatry. Two fields are available for authors (whom we refer to as “respondents”) to enter comments: one is titled “Side effects” and the other, “Comments”.

Respondents are also asked to enter some basic demographic information in separate fields, including their age, gender, diagnosis and the length of time they have been taking **the drug in question**. Some respondents volunteer information on their current dose or concurrent medications and all respondents are asked to rate the drug on a scale from 1 (most negative) to 5 (most positive). All data on www.askapatient.com are publicly available and anonymous and therefore we judged it ethically acceptable to conduct a passive analysis of the comments [12].

Analysis of comments

Before the respondents' entries were scrutinised, the authors compiled a list of possible psychoactive and physical effects associated with modern antidepressants derived from the reported adverse effect profiles of these drugs **[1-3,13]**. All comments from askapatient.com on the drugs selected for this study were then identified. The authors went through the comments initially, independently, to identify further commonly reported effects. A final list of 177 probable and possible drug-induced physical and mental effects, related both to drug ingestion and drug withdrawal, was produced by consensus.

For the final analysis, a sample of comments selected from the total number of comments posted up until 29 July 2009. **On the website, comments are ordered according to their date of entry**. At this time, there were 579 comments on fluoxetine, 703 on venlafaxine, and 1745 on the venlafaxine slow release preparation. The comments on the two preparations of venlafaxine were treated as a single set of comments. **Comments, rather than respondents, were selected as the unit of analysis, since comments could not be reliably linked to any particular individual. A small number of respondents may have entered more than one comment, but the great majority of comments were entered by different**

individuals, as evidenced by differing demographic data. To obtain roughly equal numbers of comments on each drug, we selected every fifth and every third consecutive comment on fluoxetine starting with the first (in date order), and for venlafaxine we selected every tenth consecutive comment starting with the first one. One author (LG) then coded all comments according to the final full list of effects. **Care was taken to only code effects explicitly stated to be side effects of the medications (not part of the underlying condition), and withdrawal effects were coded separately to effects experienced whilst on the medication.** The other author (JM) replicated the coding process for the last 30 selected comments for both drugs. Inter-rater reliability tests were conducted using kappa statistics. For the current analysis **we excluded physical effects, except for physical effects that had strongly apparent associations with mental effects.** We also excluded effects that were associated with drug withdrawal. We then condensed similar mental or psychoactive effects (like "emotional numbness" and "indifference") into a smaller number of broader categories (Table 2). Verbatim quotations were selected to illustrate the content of each category. The proportions of people experiencing each category of psychoactive effect, and common physical effects were computed, **with confidence intervals**, and differences in the proportions between the two drugs were tested using Chi squared tests (Table 2).

Testing associations

We were interested in exploring the association between different types of psychoactive effect. In order to do this systematically, and **to decrease the likelihood of** false positive results from conducting numerous tests, we selected the two main types of emotional effect that were identified in the data and investigated associations between these effects and other psychoactive effects that might plausibly be related,

using logistic regression analysis. We also looked at predictors of suicidal ideation. Comments on the two drugs were combined for the purpose of this analysis. We also selected verbatim quotations that provided qualitative data on the global nature of the effects of the drugs. We investigated associations between age and effects that have been associated with age in other analyses [3].

Results

Two hundred and forty two comments were analysed on venlafaxine and 226 on fluoxetine. The majority of respondents were women and **ages ranged from 15 to 71** (Table 1). The majority recorded being treated for depression, with anxiety being the next most common disorder recorded.

Table 2 shows the broad categories of psychoactive effects that were constituted and the sort of experiences that comprised them. Kappa statistics indicated good inter-rater agreement (kappa>0.7) for all the major effects.

Table 3 presents the proportions of respondents taking venlafaxine and fluoxetine who mentioned each category of psychoactive effect. The most commonly recorded subjective effect for both drugs combined was sedation, which was described by around a quarter of respondents. Activation effects, defined as feelings of increased arousal, tension, agitation, physical or mental restlessness and insomnia were described by 28% of respondents taking fluoxetine and 21% taking venlafaxine. Activating effects were not related to reports of euphoria (χ^2 0.67 [1], p=0.41), and were usually described as unpleasant. Inspecting the data suggested activating effects might be related to reports of involuntary movements like tics, twitches, “shakiness” and jaw clenching, and the Chi squared test confirmed this (χ^2 19.1 [1], p<0.001). Involuntary movements were the most commonly reported physical effect of

fluoxetine, reported by 11.5% of people taking this drug, and 9.5% of people taking venlafaxine. **Comparing the distributions of the age, respondents who mentioned activating effects were slightly younger (mean 33.8, standard deviation, s.d., 11.6) compared to those who did not (mean 36.0, s.d. 11.3), but the difference was not statistically significant (t=1.79, [185.7], p=0.08).** Reports of impaired cognition were also relatively common. Euphoria and "calmness and relaxation" were not commonly reported **and confidence intervals overlapped or were close to including zero**.

Two types of emotional effect were distinguishable. **Seventeen percent of respondents taking venlafaxine and 19% of respondents taking fluoxetine** described feelings we have classified as "emotional blunting". Twelve per cent of respondents on venlafaxine and 18% on fluoxetine attributed signs of "emotional instability" to taking the drugs, including **new or increased** anxiety, depression or mood swings, irritability, anger, aggression and disinhibition or loss of control. Increased suicidal thoughts were attributed to the antidepressant drug by 5.4% of people taking venlafaxine and 3.5% of those on fluoxetine.

Users of venlafaxine more frequently reported vivid dreams and the experience of electric shock-like sensations in the head, often referred to as "brain zaps", **which are more commonly associated with drug withdrawal, was also explicitly reported during normal drug use** (Table 3). **This result suggests rapid drug metabolism in some users may engender withdrawal effects between doses.** Impaired cognition and reduced libido were also more common among those taking venlafaxine and activation effects were more common among people taking fluoxetine, although these differences were not statistically significant.

Exploratory logistic regression, **including all variables listed in Table 4**, revealed that emotional blunting was independently associated with cognitive impairment,

reduced libido and suicidal ideation. Emotional instability was independently associated with activating effects, suicidal ideation and more weakly with age **(mean age of those experiencing emotional instability was 32.2, s.d. 11.8, compared with 36.1, s.d. 11.2 for those who did not).** Suicidal ideation was independently predicted by both types of emotional effect, but age and other psychoactive effects were not associated.

Global descriptions of the experience of taking the antidepressants, provided in the examples in Table 2, help to **illustrate** the relation between different psychoactive effects. In particular, they demonstrate how feelings of emotional blunting or indifference coexisted with arousal effects, emotional instability and suicidal thoughts.

Discussion

Limitations

Data from patient-centred websites suffers from the problem that patients may attribute effects to medication that arise from other sources, such as the underlying psychiatric problem. Effects with a physical component, like sedation and agitation, as well as various outright physical effects, can be credibly attributed to drug ingestion but cognitive and emotional effects are more difficult to ascribe to a drug with certainty in the absence of a placebo group. However, **the mental effects described on the askapatient.com website were consistent with each other**, and with the limited data reported from other sources (see below). **There is also no check for the truth of responses or the authenticity of respondents on askapatient.com. Many of these problems, however, apply to naturalistic prevalence surveys, and standard adverse event reporting systems are also unreliable, and are unlikely to**

detect less serious but unpleasant drug-induced reactions [9]. The lack of detailed descriptions of psychoactive effects from placebo controlled trials, or from volunteer studies, **which are uncontaminated by symptoms of underlying mental health problems,** makes the current data, with its large number of spontaneous and open-ended responses, an important source of information about the range of psychoactive effects induced by two modern antidepressants.

It is also difficult to assess the characteristics and motivation of people who post comments on medication websites and there is a concern that they may have unusually negative experiences of drug treatment. It is also difficult to assess how representative they are of all medication users. However, only a minority of the responses analysed described a negative experience of antidepressant medication (Ratings 1 and 2, Table 1) and the frequency with which common adverse effects were mentioned in this sample was lower than that detected in formal prevalence studies [2,14]. The mean duration of treatment was also longer than would be expected, which suggests that this sample was not skewed towards the most dissatisfied medication users, who would be expected to stop treatment within a short time. Therefore, we could see no particular indication that respondents in our current sample might be more disgruntled than other antidepressant users.

In any case, since the current study was not a prevalence study, but aimed instead, like volunteer studies, to identify the range of drug-induced mental effects, the generalisability of the sample is not crucial. Moreover, recent data from the United States suggest that the clinical characteristics of antidepressant users in general are unclear, with only a minority report a diagnosable mental illness, **for example**. Moreover, only about a third report being seen by a mental health professional, and 38% were prescribed at least one other sort of psychotropic drug,

most frequently anxiolytics [15]. Therefore **the current data may be more representative of the experience of all antidepressant users** than data from more homogenous groups, such as those that enter clinical drug trials.

The current sample had the expected excess of women over men, but users were younger than other samples [15], which would be expected from data taken from an internet site. Unfortunately, dose was infrequently recorded, but average recorded doses were within recommended therapeutic limits.

An important limitation of the current study was that we could not assess the prevalence of drug-induced effects, since the website offered only a free text format, and contained no prompt to ask respondents whether they had experienced particular adverse effects. Although some respondents appeared to list all effects they had experienced, others only mentioned one or two, without indicating whether they had experienced others.

Overview of findings

The psychoactive effects identified in the current data can be classified into two broad groups of effects: sedation, cognitive impairment, reduced libido and general emotional blunting and activation effects and emotional instability. Suicidal thoughts were most strongly related to emotional instability, but they were also associated with emotional blunting.

The effects described are consistent with other research with patients and volunteers. Sedative effects were reported by half of SSRI users surveyed recently [2], and volunteer studies confirm that SSRIs and venlafaxine produce cognitive impairment, but to a lesser degree than other sedative psychotropic drugs such as tricyclic antidepressants and benzodiazepines [16]. Emotional blunting effects of

antidepressants have received little attention, but recent qualitative research provides similar descriptions of their nature [4]. In contrast, sexual side effects of SSRIs are well documented, including reduced libido [14,17]. The current study suggests that reduced libido is not an isolated effect, but is related to general emotional blunting.

The current study confirmed the presence of "activation" effects in people taking fluoxetine or venlafaxine. Unlike stimulants, these arousal-type effects were not associated with euphoria. **In the current analysis "activating" effects were restricted to effects with a physical component, such as restlessness and signs of hyper-arousal, and these effects were associated with the clearly physical effect of involuntary movements. The current data suggests therefore that the drug-induced activating effects of these two antidepressants has a physical basis.** Feelings of emotional instability were also strongly associated with activating effects. They are often coded as "activating effects" in clinical trials [13], but may also be recorded as naturally occurring mania or hypomania. However, we felt that it was worth distinguishing the emotional component from the arousal (activating) component of the effects of SSRIs and venlafaxine, since the emotional component has not been well described to date. The category of emotional instability included increased depression, mood swings, anger and aggression attributed to the drugs, and it was associated with increased suicidal ideation and younger age. Other authors have described the dysphoric arousal state produced by SSRIs as "akathisia" and suggested that suicidal and violent impulses may occur as part of this effect [6,8,18]. Hence the current research strengthens the hypothesis that there is an emotional component to the activating effects produced by SSRIs and related drugs, that may explain their possible and still controversial link to occasional suicidal and violent ideation and behaviour. Comments made in this data and previous research [4] suggest that

emotional blunting may also be linked to suicidal ideation through reducing normal inhibitions.

The subjective effects of the antidepressants described here may impact on the symptoms of depression and other psychiatric disorders. Emotional blunting and cognitive effects may reduce the focus on depressed feelings or negative experiences, for example, and may also explain volunteer studies that suggest that antidepressants reduce the recognition of some negative emotional expressions [19]. The effects reported may also lead to the breaking of the blind in double blind trials, thereby possibly enhancing the placebo effects experienced by people in the active drug group. The data may therefore support the idea that antidepressants work through a "drug-centred" mechanism, by producing an altered mental state which impacts on depressive rating scales [20]. Elsewhere one of the authors has argued that this "drug-centred" explanation for the action of psychiatric drugs, including antidepressants, provides an alternative to the notion that they work in a "disease-centred" or disease-specific way by reversing underlying pathology [21].

Both type of emotional effect reported in this study were generally experienced as unpleasant and other research has found that these effects have an important influence on patient adherence [1]. **Further research is needed to confirm these effects, to clarify how they impact on people with depression and other diagnoses, and to identify the mechanisms which underlie the emotional and other psychoactive effects of these drugs.** In the meantime, however, patients may want to be warned that antidepressants may induce altered emotions in some users, and prescribers should also be more aware of the mental effects of antidepressants.

Conclusion

The current data found that users of two antidepressants, fluoxetine and venlafxaine reported a range of psychoactive effects, the most common being sedative-type effects, activation effects, reduced libido and both emotional blunting and emotional instability. Rarely users reported increased suicidal ideation and it was associated with both sorts of emotional effect. The psychoactive effects of antidepressants deserve further attention, both because of the direct morbidity they involve, and because of how they may impact on the symptoms of mental disorder. Improved understanding of these effects may help to clarify the mode of action of antidepressants and will help to make prescribing decisions more rational and effective.

Abbreviations

SSRI: selective serotonin reuptake inhibitor

IQR: inter-quartile range

Conflict of Interest statement

Neither author has any financial interests that are likely to be affected by the publication of this article.

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Table 1: Demographic characteristics and drug rating of respondents

Characteristics	Venlafaxine	Fluoxetine	Statistical significance of difference between drugs
Number women (%)	182 (75.8)	161 (73.5)	p=0.33*
Mean age in years (sd)	36.5 (11.6), range 15 to 67	34.3 (11.1), range 15 to 71	p=0.04**
Median duration of treatment in months (IQR)	8 (1.5-24)	5 (1.8-24)	p=0.88***
Mean daily dose in mg (sd)	145.6 (99.5) range 15-600 (n=79)	26.4 (14.4) range 1.5-60 (n=47)	
Mean overall drug rating (sd) (5 most positive, 1 most negative)	3.2 (1.5)	3.5 (1.4)	p=0.03**
Rating 4-5 Rating 3 Rating 1-2	49.2% 19.4% 31.4%	58.4% 15.0% 26.6%	p=0.13*
Main recorded disorders (%)****			
Depression	181 (74.8)	168 (69.9)	p=0.91*
Anxiety	96 (39.7)	72 (31.9)	p=0.07*
Panic Disorder	17 (7.0)	15 (6.6)	p=0.87*
Bipolar	8 (3.3)	5 (2.2)	p=0.47*
Pain Management	8 (3.3)	5 (2.2)	p=0.47*
OCD	4 (1.7)	30(13.3)	p<0.001*
Eating disorder	3 (1.3)	10 (4.4)	p=0.046*
PMS/PMDD	1 (0.4)	18 (8.0)	p<0.001*
More than one problem	91 (37.2)	96 (42.5)	p=0.28*

* Chi squared test
**t test
*** Mann Whitney U tests used because distributions deviated from the Normal distribution
****Co-morbidity of disorders was often recorded (especially Depression and Anxiety), explaining percentages adding up to over 100%

Table 2: Major categories of psychoactive effects associated with fluoxetine and venlafaxine reported by respondents on askapatient.com

Category of effect	Illustrative comments	Kappa statistic for agreement between raters
Sedative effects	"sleepiness" (F95), "constant fatigue" (V140), "lethargy" (F330), "reduced energy level" (V540), "feeling groggy" (V560)	0.87 p<0.001
Reduced libido	"decreased libido" (VXR1540), "killed my sex drive" (F 435)	1.0 p<0.001
Activation effects	"jitteriness" (F535), "nervousness" (F420, VXR30), "inability to sit still" (F415), "jittery legs" (F270), "restless" (F285), "agitated" (VXR1260)	0.80, p<0.001
Emotional blunting	"flat mood" (VXR 1540), "unable to cry very often" (F195), "numb," "blank" (V570), "no motivation" (VXR 460), "lack of interest" (VXR 1470), "distanced from life" (F165), loss of "humour" (F275), "less creative, less motivated, and it seems less me" (F 520)	0.80 p<0.001
Impaired cognition	"forgetfulness, confusion" (F326), "difficulty concentrating and remembering…fogginess" (F95), "fuzzy thinking" (VXR 1270), "slowness..lack of clarity" (V140)	0.78 p<0.001
Vivid dreams	"vivid dreams" (V60), "weird dreams" (F190), "bad nightmares" (V320) "the dreams are bothersome, unlike in character and intensity to any dreams I've had previously" (F520).	1.0 p<0.001
Emotional instability	"incredible anger" (F185), "bursting into tears for no apparent reason and not being able to control myself" (VXR1480), "severe emotional swings" (V380), "made me moody and emotional" (F495), "a very short fuse" (F293), "disinhibited" (F320)	1.0, p<0.001
Increased suicidal thoughts	"suicidal thoughts" (VXR 1460) "suicidal thoughts, feelings of death" (F 543)	1.0 p<0.001
Electrical sensations not related to withdrawal	"brain zaps" (VXR 1600), "peripheral electrical feelings" (VXR 480), "brain pains" (VXR 1700), "electrical shock in my hands" (V 70)	0.73, p<0.02
Relaxation and calmness	"feelings of peacefulness" (F195) "made me feel calm" (VXR 780)	1.0 (p<0.001)
Euphoria	"somewhat of a euphoric sensation" (VXR 420)	No cases in

	"made me feel unnaturally high" (F 228)	reliability sample*
Global descriptions of effects	"Severe emotional swings… crying spells, uncaring and emotionally flat most of the time" (V380). "Fuzzy memory..loss of libido.. general numbness/mental blankness…memory loss" (VXR 1050). "Sleepy all the time, suicidal thoughts, irritability, don't care about anything" (VXR 1460). "Total loss of libido, sometimes suicidal, loss of appetite, inability to care about anything, mood swings" (F225). "Increased anxiety initially, borderline panic, mild in(para)somnia, listlessness and lethargy" (F 330). "Sleepiness, memory loss, loss of sex drive" (F370). "Made me anxious yet disinhibited, so I didn't care what others thought of my behaviour" (F320).	

*Kappa cannot be calculated when the identified cases equals zero.

Table 3:

Proportion of respondents reporting psychoactive effects of fluoxetine and venlafaxine

Category of Effect	Venlafaxine N=242 (%; ±95% confidence interval)	Fluoxetine N=226 (%; ±95% confidence interval)	Statistical significance for Chi squared test for difference between drugs (with one degree of freedom)
Sedative effects	67 (27.7; ±5.6)	56 (24.8; ±5.6)	p=0.48
Reduced libido	57 (23.6; ±5.4)	38 (16.8; ±4.9)	p=0.07
Activation effects	50 (20.7; ±5.1)	64 (28.3; ±5.9)	p=0.05
Emotional blunting	47 (19.4; ±5.0)	39 (17.3; ±4.9)	p=0.55
Impaired cognition	46 (19.0; ±4.9)	29 (12.8; ±4.4)	p=0.07
Vivid dreams	43 (17.8; ±4.8)	11 (4.9; ±2.8)	p<0.001
Emotional instability	30 (12.4; ±4.2)	40 (17.8; ±5.0)	p=0.10
Increased suicidality	13 (5.4; ±2.8)	8 (3.5; ±2.4)	p=0.34
“Brain zaps” not related to withdrawal	12 (5.0; ±2.7)	0 (0)	p<0.001
Relaxation and calmness	5 (2.1; ±1.8)	2 (0.9; ±1.2)	p=0.30
Euphoria	1(0.4; ±0.8)	4 (1.8; ±1.7)	p=0.15

Table 4: Logistic regression analysis

	Emotional Blunting	Emotional Instability	Suicidal ideation
Age	p=0.16	p=0.04	p=0.64
Cognitive impairment	p=<0.001	p=0.10	p=0.95
Reduced libido	p=0.003	P=0.26	p=0.54
Activation Effects	p=0.06	p<0.001	p=0.24
Sedative effects	p=0.15	P=0.07	0.16
Emotional blunting		p=0.92	p=0.003
Emotional instability	p=0.91		p<0.001

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