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The interpersonal adverse effects reported by 1,008 users of antidepressants; and the incremental impact of polypharmacy

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Abstract

Antidepressant drugs are being prescribed at ever increasing rates internationally, despite marginal benefit compared to placebo and a range of adverse effects. Most studies of adverse effects focus on biological phenomena. This article presents the results of an online survey of 1,008 self-selected anti-depressant users in Britain, which asked about five adverse effects in the interpersonal domain. The most commonly reported among participants who took only antidepressants were: Sex Life – 43.7%, Work or Study – 27.0% and Social Life – 23.5%. These rates of interpersonal adverse effects were even higher for the 52% of participants who were also taking one or more other psychiatric drugs. Only about a half (48%) felt they had been given enough information about side effects by the prescriber. Those initially prescribed medication by a psychiatrist were more likely to be on several types of drugs and reported more adverse effects than those whose prescriber was a General Practitioner (GP). Researchers and prescribers are encouraged to pay greater attention to interpersonal adverse effects.

Keywords:
Depression
Antidepressants
Side effects
Polypharmacy

1. Introduction

Despite already being extremely high, prescription rates for antidepressants (ADs) continue to rise (Ilyas and Moncrieff, 2012; O.E.C.D., 2016). In 2015, England had 61.0 million prescriptions for a population of 54.8 million. This was more than double the number for 2005. The annual rise in 2015, of 3.9 million more prescriptions than in 2014, was the largest increase of all drug categories. In 2015 ADs cost the National Health Service £780,000 per day (Health and Social Care Information Centre 2016). In Australia antidepressant use doubled between 2000 and 2014, and antidepressants are now the most commonly used of all medications, being taken by 10% of adult Australians each day (Davey and Chanen, 2016; OECD, 2016). In the USA ADs had already become the most widely prescribed drug category by 2005, with 10% of people over the age of six prescribed ADs annually (Olfson and Marcus, 2009). By 2012 this had increased to 13% of adults (Kantor et al. 2015), or one in eight people.

These very high prescription rates, and continual increases, are taking place despite concerns about efficacy and safety. Placebo effects in response to being given ADs have been well documented (Read et al., 2015). Fifteen years ago it had already been identified that less than half of trials find ADs superior to placebo (Khan et al. 2002). It has subsequently been established that properly blinded and independent (i.e. non drug industry) studies are particularly unlikely to find any difference to placebo (Khan and Brown 2015; Moncrieff 2015). A meta-analysis found that 'the overall effect of new-generation antidepressant medications is below recommended criteria for clinical significance' (Kirsch et al., 2008), with greater benefit than for placebo found only for 'patients at the upper end of the very severely depressed category'. Other reviewers, however, failed to find a significant effect of depression severity on drug vs. placebo difference (Rabinowitz et al., 2016). The most recent

meta-analysis reviewed 131 randomised placebo-controlled trials involving 27,422 people and found that the overall effect size did not reach the threshold for 'clinical significance'. They also found no difference between those taking ADs or placebos in reducing suicide, suicide attempts or suicide ideation (Jakobsen et al., 2017). While not all researchers would agree with them (e.g. Rabinowitz et al., 2016), these reviewers concluded that 'The harmful effects of SSRIs versus placebo for major depressive disorder seem to outweigh any potential small beneficial effects' (Jakobsen et al., p. 23).

Studies of these harmful effects typically record primarily or exclusively biological or medical effects. The 2017 meta-analysis, for example, defined serious adverse events as 'medical events that were life threatening …' (p. 4). Of the 84 other adverse events reported by the meta-analysis to have been studied at least once, almost all were biological/medical reactions. The eight adverse effects most often assessed in the 131 placebo controlled studies (all found to be significantly more common in AD recipients than in placebo recipients) were: nausea (78 studies), headache (72), dry mouth (73), insomnia (69), somnolence (59), diarrhea (58), dizziness (55) and constipation (50). Both the 'Antidepressant Side-Effect Checklist' (Uher et al., 2009) and the 'Patient-Rated Inventory of Side Effects (PRISE)' (Adkins et al., 2012) focus almost exclusively on these bio-medical phenomena and fail to address adverse effects in the psychological or interpersonal domain. Such an array of unwanted physical symptoms is not to be minimised. They may be particularly distressing when one is already depressed. It is a concern, however, that there are very few studies, and no placebo-controlled studies, examining the negative effects of ADs in the equally important interpersonal and personal domains.

A 2013 review of the few, relatively small scale, studies of the subjective experiences of AD users (Gibson et al., 2014) identified multiple adverse effects in the psychological, emotional and interpersonal domains. These included a reduction of positive and negative

emotions, emotional detachment, a belief that ADs prevent natural sadness, personality changes, harmful effects on relationships, caring less about self and others, fear of addiction, and suicidality (Givens et al., 2006; Liebert and Gavey, 2008; Pestello and Davis-Berman, 2008; Price et al., 2009; Goldberg and Moncrieff, 2011). The largest survey of AD users to date (1,829 New Zealanders) identified very high rates of adverse effects in the personal and interpersonal domains, including: sexual difficulties (62%), feeling emotionally numb (60%), feeling not like oneself (52%), agitation (47%), reduction in positive feelings (42%), suicidality (39%), and caring less about others (39%) (Read et al., 2014).

There are surprisingly few studies of what prescribers tell their patients about the adverse effects of ADs. Of 107 patients of GPs in Britain, 41% could not recall any discussion about adverse effects (Byng et al., 2007). Similarly, 36% of AD users in the large New Zealand survey were told nothing about any adverse effects; and, more specifically, fewer than 1% were told about emotional numbing or reduction in positive feelings, and none were told about feeling less like themselves or caring less about other people (Read et al., 2014).

None of the studies reported above, whether placebo controlled trials or surveys of the subjective experience of AD users, have measured the effects of the use of other psychiatric medications simultaneously with ADs on rates of adverse effects.

1.1 Aims of the study

This study, therefore, reports a survey of over 1,000 AD users in the UK who were asked about five types of adverse effects in the interpersonal domain plus 'physical health, about whether they were told about adverse effects at the time of prescribing, and about their use of three other types of psychiatric medication.

2. Method

2.1 Instrument

The *Medication for Mental Health Survey* asks adult users of psychiatric medications a range of questions, primarily with yes/no or multiple choice responses, about perceived effectiveness, side effects and the processes of commencing and coming off four types of medication: 'Antidepressants', 'Antipsychotics', 'Mood stabilisers (including lithium)'and 'Tranquilisers or sleeping pills'. The online survey was designed by *Mind*, the mental health charity for England and Wales (www.mind.org.uk), to inform one of a series of articles by *The Times* newspaper about the side effects of medications taken for mental health problems. This online survey, which used *Survey Monkey,* was advertised on the *Mind* website for four weeks in 2012, during which time it was also sent to all *Mind* members by email, and posted on social media including *twitter* and *facebook*.

2.2. Sample characteristics

A total of 1,797 completed the survey. This paper reports the responses of the 1,008 who were taking antidepressants when they completed the survey. The majority were women (76.2%). Of the 995 who gave their age, 12.6% were 18-24 years old; 28.8% were 25-34; 30.8% were 35-44; 18.2% were 45-54; 8.4% were 55-64; and 1.2% were 65 or older. The majority (87.5%) classified themselves as 'White British'; while other groups of six or more participants were: 'White Irish' (3.0%); 'Other white background (4.4%) and 'Black British Caribbean' (0.6%). The initial prescriber had been a GP for 652 (64.7%) and a psychiatrist for 350 (34.7%) (six people could not remember). The majority (91.7%) had been taking ADs for at least 6 months, 69.7% for at least two years, 44.8% for five or more years and 24.4% for more than ten years. About one in four (24.5%) were members of Mind.

Overall level of satisfaction with antidepressants is an important contextual characteristic of the sample and is therefore presented here. The responses, of those who had taken only antidepressants (n = 484), to the question 'How effective do you feel your current medication is in helping to manage your mental health problem' were: 'Completely' - 3.9%'; 'Very' - 30.4%; 'Fairly' - 49.4%; 'Not very' - 13.7%; Not at all' - 2.6%.

2.3. Data analysis

A score (0-4) for overall severity of adverse effects was calculated using the following scoring: 'None' = 0; 'Some side effects but they have gone now' = 1; 'mild' ongoing = 2; 'moderate' ongoing = 3; 'severe' ongoing = 4. A score (0-4) for perceived efficacy was calculated using: 'Not at all effective' = 0; 'Not very effective' = 1; 'Fairly effective' = 2; 'Very effective' = 3; 'Completely effective' = 4.

Chi square (X^2) was used to examine possible relationships between categorical variables, and Spearman rank correlation (*rho*) was utilised for ranked, non-parametric variables. A two-tailed t-test for independent samples measured the difference in the mean number of medications used by those for whom the original prescriber was a psychiatrist or a GP.

3. Results

3.1. Adverse effects

3.1.1 Antidepressants only

Of the 484 who had taken *only* antidepressants and were still taking them, 455 responded to the question 'Do you have side effects as a result of taking your medication and, if so, how severe are they?' The majority (391; 85.9%) reported side effects. While 125 (27.5%) endorsed 'Some side effects at first but they have gone now', about twice as many

(266; 58.4%) were still experiencing side effects at the time of survey completion. Most of these 266 described the side effects as 'mild' (170; 63.9%); with 85 endorsing 'moderate' (32.0%) and 11 (4.1%) ticking 'severe'. Only 64 of the 455 (14.1%) had experienced no side effects at any time.

Participants were asked to respond (yes/no) to whether they had experienced each of six types of adverse effects. Table 1 shows that by far the most frequently endorsed of the six was Sex Life – 199 (43.7%); followed by Work or Study – 123 (27.0%); Physical Health – 122 (26.8%); and Social Life – 107 (23.5%). At least one of the five interpersonal effects (i.e. excluding Physical Health) was reported by 274 (60.2%) of the participants; 151 (33.2%) reported two or more and 96 (21.1%) reported three or more.

Overall severity of side effects was negatively related to perceived efficacy of the antidepressants (*rho* = 0.37; $p < .0001$). Perceived efficacy was also negatively related (at the $p < .0001$ level) to each of the six types of side effect, with the strongest relationship being between an adverse effect on Close Relationships and lower perceived efficacy of the medication ($X^2 = 95.00$). Neither age nor gender was related to overall severity, or to specific types, of adverse effects.

Overall severity was positively related to how long people had been taking ADs ($X^2 = 41.09$, $p = .004$). Of the six adverse effects duration of medication was only related to Physical Health ($X^2 = 25.22$, $p < .0001$), and Sex Life ($X^2 = 13.32$; $p = .021$) (and not to any of the four other interpersonal effects).

The initial prescriber being a psychiatrist, rather than a GP, was positively related to overall severity of adverse effects ($X^2 = 33.99$, $p < .001$). Of those prescribed ADs by psychiatrists, 32.3% reported moderate or severe side effects, compared to 18.2% of those prescribed by a GP. The prescriber being a psychiatrist, rather than a GP, was also positively related to four of the six adverse effects at the $p < .001$ level or beyond: Social Life, Work or

Study, Independence and Physical Health (but was unrelated to Close Relationships or Sex Life).

* * * Table 1 about here * * *

Participants were also asked 'Is there anything else you would like to tell us about your experience of taking medication?' Of the 244 who wrote something, 69 (28.3%) discussed negative effects, including how the adverse interpersonal effects can result from the adverse biological effects, and how it is sometimes hard to separate the effects of the drugs from the effects of feeling depressed. For example:

> Weight gain and sweating causing social embarrassment.
>
> When taking a high dose I was unable to meet up with friends and such due to feeling drowsy all of the time.
>
> I hate it. It makes me emotionally flat - for example, I had to stop taking them after a recent family bereavement to make sure I was able to cry at the funeral.
>
> The drugs make me totally disconnected from everything and lifeless.
>
> My medications can make me drowsy and I lost a job because they thought I was drunk or taking drugs.
>
> It makes it hard to concentrate at work and makes learning new things very difficult.
>
> I think it is causing fatigue, amongst other things so I have had to drop my hours at work from full-time to 3 days a week.
>
> It made me very tired and ill to start with which effected (sic) my University studies at the time.

I get tiredness and low concentration and have had to stop/suspend university (awaiting a decision). This is a side effect I feel I have to accept from a choice I have made myself but wish it was not a choice I had to make.

It affected my sexual relationship with my partner as I had no desire to have sex and we are still feeling the effects of this now as he is nervous to ask after knowing that I wasn't interested for such a long time.

It is very hard to separate the effects of the meds and the effects of the illness.

I don't know whether I'm unable to work or study, not up to socialising, etc., because of the medication, because of the low mood, or both.

3.1.2 Polypharmacy

An additional 524 participants were using antidepressants but were also using one or more of three other types of psychiatric medication, as follows: 'tranquillisers or sleeping pills' - 314; 'antipsychotics' - 267; and 'mood stabilisers (including lithium)' - 246. Thus of all the participants taking antidepressants (n = 1,008), just over half (524, 52.0%) were also taking at least one other type of psychiatric medication. One hundred and sixty one (16.0%) were taking two additional types; and 74 (7.3%) were taking three additional types.

Neither age nor gender were related to polypharmacy (the simultaneous use of two or more types of psychiatric medication). Length of time taking ADs was strongly predictive of polypharmacy ((X^2 = 69.94; p < .0001). The mean number of additional drugs taken was strongly predicted by whether the original prescriber was a psychiatrist (1.35) rather than a GP (0.53) (t = 13.33, df = 609.3, p < .0001). When a psychiatrist was the prescriber, 42.6% of participants were taking two or three other types of medications beside antidepressants, compared to 12.6% of those prescribed antidepressants by a GP.

The number of types of medication (from one to four) was significantly correlated with overall severity of side effects (*rho* = .26, p < .001). The number of medication types was also related to each of the six types of adverse effect, at the p = .001 level or beyond, with X^2 ranging from 21.69 (for Sex Life) to 98.15 (for Work or Study). For example, while 43.7% of those on antidepressants alone reported an adverse effect on their sex life, this was the case for 54.0% of those on antidepressants plus one other psychiatric medication, and for 63.5% of those on three additional medications. Table 1 shows that polypharmacy more than doubled the rates for the other five adverse effects. For example Work or Study was effected for 27.0% of those taking only ADs and 68.9% of those on ADs plus all three other types of drugs.

The number of drug types being taken was negatively related to perceived effectiveness of the drugs (*rho* = - .093; p = .003). Of participants taking only antidepressants 33.4% rated their 'current medication' as 'completely' or 'very' effective, compared to 28.0% of those on two additional medications and just 17.6% of those on three extra drugs.

3.2. Information

In response to the question 'Do you feel that you were given enough information about the medication you were taking, including side effects and withdrawal?' those taking only antidepressants replied as follows: 234 (48.4%) ticked 'Yes'; 195 (40.4%) ticked 'No'; and 54 (11.2%) ticked 'I can't remember/ I don't know'.

Age was positively related to not been given enough information (X^2= 18.3; p = .019). Exactly half of 18-24 year olds stated they had been given enough information, compared to 32.3% of those aged 55 or older. Men (53.5%) were significantly more likely than women (46.8%) to report been given enough information (X^2= 152.0; p < .0001). Information giving was unrelated to whether the prescriber had been a GP or a psychiatrist.

Responses to the open ended question included:

The side-effects weren't explained very well by the prescribing GP. Anorgasmia is a particularly bad side-effect.

I wasn't told of all the side effects; in fact, when I researched them myself and then told my doctor, she hadn't got a clue it could affect you in the way it affected me.

Side effects are seldom discussed. Only one of the five psychiatrists who has treated me over 14 years has explained possible side efefcts. (sic)

Would of (sic) liked to hear more about side effects. . . . . I had to find out lots of information myself when I was in a difficult anxious state.

Full information about the drug (pros AND cons) should be emphasised to the patient before prescription.

In reality psychiatrists refuse to answer questions and refuse to accept or discuss side effects.

Really not enough information about withdrawal effects or side effects.

The first GP I went to actually told me in all seriousness that there were no known side effects! I'm not retarded. A quick read through the leaflet put his misinformation straight.

Medication makes you emotionally numb, forgetful and restricts your emotional responses to the point where it can be frustrating as you can't express yourself fully. These are the 'side-effects' that you don't get told about but are also the reasons for not wanting to go back on medication again.

4. Discussion

4.1. Adverse effects

This survey, the second largest to date, confirms that side effects are very common when taking ADs. The majority (85.9%) of the participants who only took ADs experienced some degree of side effects, with 36.1% of these describing the effects as either moderate or severe. Furthermore, it seems that when doctors tell patients that side effects will be relatively short lived this is accurate for about a third of patients in this sample. Only 125 of the 391 who experienced side effects ticked 'Some side effects at first but they have gone now' (31.0%), and the remaining 69.0% were still experiencing side effects when they filled out the survey.

This study also suggests that adverse effects in the interpersonal domain, that have until recently received relatively little attention, are actually extremely common. Over half (60.2%) reported at least one of the five interpersonal effects measured and a third reported two or more. Adverse effects on 'Sex Life' were the most common in both the current study (43.7%) and the large New Zealand survey (62.3%) (Read et al., 2014). The current study's findings about Social Life (23.5%) and Close Relationships (20.9%) can be compared to the 38.8% of New Zealand AD users reporting 'caring less about others'. Furthermore, interviews with 38 British AD users found that 'Many participants reported not caring as much about others, such as during social interactions, by being less sensitive or courteous towards other people. In addition, many described reduced concern for others' feelings'. (Price et al., 2009, p. 215). To the best of our knowledge this is the first survey to have asked directly about effects on work or study; and the 27.0% response rate warrants serious attention from both prescribers and researchers.

The current study did not replicate the findings of the New Zealand survey that sexual difficulties and caring less about others were significantly more common in men than women.

The higher rates of adverse effects among those prescribed ADs by psychiatrists, rather than GPs, may be partially understood in terms of the greater degree of polypharmacy utilised by psychiatrists.

It must be noted that despite all these adverse effects, some of which were crushingly severe, 84% of respondents found the drugs to be at least 'fairly effective'. This replicates the larger survey of AD users in New Zealand, which found that besides experiencing the adverse effects listed above 83% believed the ADs had reduced their depression to some extent (Read et al., 2014). This mixed experience of, and ambivalence towards, ADs on the part of many users has been further illustrated in the qualitative comments of both the New Zealand respondents (Gibson et al., 2016) and of the participants of several smaller scale studies involving interviews with AD users (Gibson et al., 2014). While this is usually understood in terms of a straightforward 'trade-off' between positive and negative effects, it is also possible that some of these seemingly different effects are the same thing, or at least rather similar. In reducing the depression the drugs may also be reducing all feelings and thereby replacing painful feelings with an empty emotional void, both personally and, as a further consequence, interpersonally. In the New Zealand study 60% reported feeling 'emotionally numb' as a result of the ADs. (Read et al., 2014).

The apparent contradiction between the very high rates of perceived efficacy, in both the current and NZ studies, and the low rates of actual efficacy compared to placebo in the research literature, is somewhat easier to explain. Many people do feel less depressed when taking ADs but it seems this is primarily because of the expectation raised by the processes involved in prescribing and taking the pills rather than by the chemicals therein. In the New Zealand study one of the strongest predictors of perceived efficacy was the perceived quality of the relationship between the prescriber and the patient (Read et al., 2015).

4.2. Polypharmacy

More than half of the participants taking ADs were also taking one or more other type of psychiatric medication. Polypharmacy has increased dramatically over the past three decades (Preskorn and Flockhart, 2006). A 2002 review reported that studies prior to 1980 had found that, on average, 52% of people receiving psychiatric treatment were on more than one medication, and that this had risen to 80% for studies in the 1990s (Rittmannsberger, 2002). A 2009 study found that up to one third of psychiatric outpatients were on three or more psychiatric drugs (Mojtabai and Olfson, 2010). A 2013 review found that the prevalence of polypharmacy in psychiatry varies between 13%-90% and that the practice was still 'increasing rapidly' (Kukreja et al., 2013, p. 82). The finding, in the current study, that the most common combination was ADs and tranquillisers is not new (e.g. De las Cuevas and Sanz, 2004).

Despite it's rapid increase polypharmacy cannot be described as an evidence-based approach. There have been very few rigorous studies evaluating the benefits or risks of using two or more psychiatric drugs simultaneously (Muscatello et al., 2011; Kukreja et al., 2013). The 2013 review concluded:

> While evidence for the added benefit of psychiatric polypharmacy is limited, there is growing evidence regarding the increased adverse effects associated with such combinations. Concerns with polypharmacy include not only possibilities of cumulative toxicity and increased vulnerability to adverse events but also adherence issues which emerge with increasing regimen complexity. Combinations of drugs may lead to various pharmaco-dynamic and pharmaco-kinetic interactions. Presence of one drug alters the nature, magnitude, and/or duration of the effect of another drug. (Kukreja et al., 2013, p. 90).

Thus the finding of the current study that polypharmacy was very strongly related to adverse effects in general is not new. This is the first study, however, to demonstrate this relationship in the domain of *interpersonal* adverse effects. Table 1 demonstrates the strength of the relationship, which is highly significant, both statistically and in terms of the consequences for people's social and occupational lives.

Another new finding is the greater use of polypharmacy by psychiatrists. The current survey did not generate data that might explain this phenomenon. One might speculate that it is partly because psychiatrists see more severe and complex cases, but there is little evidence that polypharmacy is an effective approach to such cases. Further research into why one profession uses polypharmacy more than another would, therefore, be important. Similarl,y the relationship revealed in the current study between polypharmacy and reduced perceived efficacy would be worthy of replication and further investigation.

4.3. Information

The finding that 40.4% could not recall being told anything about adverse effects is similar to the 41% among 107 patients of GPs in Britain (Byng et al., 2007) and the 36% of AD users in the large New Zealand survey. The finding that older people are less likely to be told about adverse effects should be considered in the context of older people being even more likely than the rest of the population to be prescribed ADs, at lower levels of depression and for longer periods of time (Read et al., 2016).

4.4. Implications

Researchers, and the designers of adverse effect checklists in particular, need to pay greater attention to side effects that fall beyond the bio-medical domain. These include not only the interpersonal effects identified both here and in the larger New Zealand survey, but

also the emotional numbing and decrease in positive feelings not studied here but identified elsewhere (Byng et al., 2007; Gibson et al., 2014; Read et al., 2014).

In order to conform to the ethical principle of informed choice, prescribers need to inform all potential AD recipients not only of the possible biological adverse effects but also of the very high chance of difficulties in the social and occupational spheres of life. Prescribers should identify, and avoid, any temptation not to inform patients about adverse effects because of their age or gender. Providing full information, to all patients, will help people understand what is happening to them if these adverse events eventuate. Without this knowledge it can be even more distressing to have one's sexual and social life deteriorate or one's work or study world become problematic. Being clearly warned about the full range of potential adverse effects, biological, personal and interpersonal, may also reduce the number of people who begin to take ADs unnecessarily. Sharing the findings of the recent reviews and meta-analyses summarised earlier may further reduce unnecessary exposure to this broad array of adverse effects, some of which can be depressing.

It seems that the polypharmacy, or 'cocktail', approach to emotional distress continues to be far too common. This appears to be particularly prevalent among psychiatrists, 43% of whose patients were on three or more types of medication. Hopefully the strength of the findings in this study linking this approach to large increases in rates of adverse effects might discourage this practice. The fact that more drugs was linked with lower perceived efficacy may be persuasive for some.

4.5. Limitations

This is a self-selected, convenience sample and may not, therefore be representative of AD users in general. Black and ethnic minority groups, for example, are underrepresented. It is also possible that people who have had negative experiences with ADs may be more

motivated to complete online surveys on the topic. However, the fact that 83.7% found their ADs at least 'fairly effective' suggest that this may not have been the case in this study.

Some of the questions, for example those regarding information received about adverse effects, rely on recall of events that occurred several years ago, and may, therefore, be less than completely accurate. Furthermore, only broad medication types were captured (rather than specific drugs) and no information on dosage was gathered.

Table 1. Relationship between six adverse effects and the number of types of psychiatric drugs taken in addition to antidepressants

	Number of types of psychiatric drugs in addition to antidepressants			
Adverse effect on…	0 (n = 455)	1 (n = 289)	2 (n = 161)	3 (n = 74)
Sex life	43.7%	51.9%	54.0%	63.5%
Work or study	27.0%	42.2%	61.5%	68.9%
Physical health	26.8%	39.1%	56.5%	68.9%
Social life	23.5%	32.5%	54.0%	59.5%
Close relationships	20.9%	31.9%	42.9%	45.9%
Independence	10.5%	19.0%	33.5%	36.5%

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