

# Psychiatric outcomes 10 years after treatment with antidepressants or anxiolytics

Ian Colman, Tim J. Croudace, Michael E. J. Wadsworth, Diana Kuh and Peter B. Jones

## Background

Antidepressants and anxiolytics have demonstrated short-term efficacy; however, little is known about the long-term effectiveness of these drugs.

## Aims

To investigate long-term psychiatric outcomes following antidepressant and/or anxiolytic use during an episode of mental disorder in mid-life.

## Method

Members of the 1946 British birth cohort were assessed for symptoms of depression and anxiety at age 43. Among 157 with mental disorder, those using antidepressants and/or anxiolytics were compared with those not using medications on psychiatric outcomes at age 53.

## Results

Use of antidepressants or anxiolytics was associated with a lower prevalence of mental disorder at age 53 (odds ratio (OR)=0.3, 95% CI 0.1–1.0) after adjustment for eight variables in a propensity-for-treatment analysis. Only 24% of those being treated with medications at age 43 were still using them at 53.

## Conclusions

Use of antidepressants or anxiolytics during an episode of mental disorder may have long-term beneficial effects on mental health. This may be because of a demonstrated willingness to seek help rather than long-term maintenance therapy.

## Declaration of interest

None. Funding detailed in the Acknowledgements.

Persistent or recurrent symptoms are common features of the long-term course of depression and anxiety.<sup>1,2</sup> Maintenance therapy with antidepressants has been shown to prevent subsequent relapses of depressive episodes but this evidence is primarily based on randomised controlled trials of relatively short duration of up to 12 months; little is known about longer-term effects.<sup>3</sup> Furthermore, these trials often have strict inclusion criteria that exclude individuals with comorbid illnesses, with suicidal ideation and those who present primarily with somatic symptoms.<sup>4</sup> Population-based samples, followed longitudinally, may be helpful in clarifying whether the short-term efficacy demonstrated in clinical trials extends to long-term effectiveness in the general population. The objective of the present study was to assess the long-term effect of antidepressant or anxiolytic use during an episode of mental disorder in mid-life, using a propensity score approach to account for non-random allocation to treatment.<sup>5</sup>

## Method

### Participants

Participants were members of the Medical Research Council National Survey of Health and Development (NSHD). This is an ongoing longitudinal study of 5362 individuals who formed a stratified sample of babies born in England, Scotland or Wales during the week of 3–9 March, 1946. The sample has been prospectively studied on 21 occasions up to age 53 years. Comparisons with census data show that those remaining in the cohort ( $n=3673$  at age 53) are broadly representative of all British-born adults currently resident in England, Scotland and Wales.<sup>6</sup>

The Psychiatric Symptom Frequency (PSF) scale, a questionnaire that records the frequency and intensity of common symptoms of anxiety and depression over the preceding year,<sup>7</sup> was administered at age 43 ( $n=3156$ ). The participants used for this study were those who scored 30 or higher on the PSF, a cut-off that yields a prevalence of approximately 7% of the cohort

at the time. We also report briefly on a second sample with sub-threshold mental disorder, who scored between 23 and 29 on the PSF.<sup>8</sup>

### Psychiatric treatment

Survey members reported prescription medication use to a nurse interviewer at age 43. This study describes outcomes associated with the use of anxiolytics (British National Formulary (BNF) Section 4.1.2) and antidepressants (BNF Section 4.3).<sup>9</sup>

### Outcomes of drug treatment

Primary outcome: mental disorder

The primary outcome was mental disorder at age 53 as measured by the 28-item General Health Questionnaire (GHQ), which focuses on self-reported symptoms of anxiety and depression, and associated psychosocial dysfunction, in the preceding 4 weeks.<sup>10</sup> The cut-off used for mental disorder was a score of 11 or higher (most severe 7%).

Secondary outcomes: associated psychiatric symptoms

A limited number of secondary outcomes were also considered. These included a broader definition of mental disorder encompassing sub-threshold symptoms (GHQ score of 7 or higher); self-reported sleeping difficulties; alcohol misuse based on the CAGE questionnaire;<sup>11</sup> and symptoms of psychosis based on four-items from a standard psychosis screening questionnaire.<sup>12</sup>

### Factors associated with treatment

Numerous factors were considered for possible associations with treatment with psychotropic medications during an episode of mental illness. Factors were also selected on the basis that they could be plausibly associated with prognosis of mental illness. In particular, we focused on factors associated with severity of symptoms and history of mental illness, since both symptom severity<sup>13,14</sup> and a history of symptoms<sup>14,15</sup> are associated with

long-term prognosis in depression, and both factors are also associated with treatment during an episode of mental disorder.<sup>16</sup>

#### Current symptom severity

Survey members were considered to have severe symptoms if they scored 54 or higher on the PSF (top 15.8% of those with mental disorder); suicidal ideation if they reported during the PSF they had 'thought about taking their own life'; sleep difficulties if they reported trouble sleeping; and alcohol misuse if they responded positively to two or more items on the CAGE screening questionnaire.<sup>11</sup>

#### History of mental illness

Survey participants were considered to have mental disorder at age 36 if they scored five or higher on the Index of Definition for the Present State Examination in 1982.<sup>17,18</sup> Treatment between age 16 and 36 was based on in- and out-patient hospital records and physician records.<sup>19</sup> Psychiatric hospitalisation up to age 43 was based on hospital records that included any admissions for mental disorder (ICD-9 codes 290-314, and ICD-10 codes F10-F69 and F90-F98)<sup>20,21</sup> or suicidal behaviour (ICD-9 codes E950-E959, and ICD-10 codes X6000-X8499). Finally, participants were asked at age 43 if they had ever suffered from 'nervous trouble'.

### Statistical analysis

Observational studies suffer from one crucial drawback in comparison with randomised controlled trials: individuals who receive treatment may differ, in clinical or social factors, from those who do not, and these differences may affect prognosis, thereby confounding any observed differences in outcome.<sup>22</sup> Naturalistic study designs must, therefore, be analysed using methods that can address these selection-to-treatment elements in order to estimate the actual impact of treatment that would have been generated by a randomised design.

One method that is now widely used for this purpose is the propensity score approach.<sup>5</sup> A propensity score is the probability of an individual being treated, calculated from a logistic regression in which all available variables likely to be associated with treatment are entered into a model predicting treatment.<sup>22</sup> Given that the objective is to balance as many covariates as possible that might be related to treatment or prognosis between the treated and untreated groups, it is desirable to include as many predictors as possible in the calculation of the propensity score.<sup>22</sup> Consequently, this study considered the eight variables described above.

If two individuals have the same probability of being treated (i.e. same propensity score), but one has been treated and the other has not, then it is as if they have been randomly assigned

to treatment, assuming that no unmeasured confounders exist.<sup>5,22</sup> If no differences exist between covariates within quintiles of the propensity score, then any overall differences in the covariates can be considered 'ignorable' as long as the analysis matches on the propensity score.<sup>22</sup> In other words, if all covariates are balanced between the treatment and non-treatment group after adjusting for the propensity score, then any observed differences between the groups should be attributable to the effects of treatment. This study used logistic regression to adjust for the propensity score in the analysis of the long-term effects of treatment with antidepressants or anxiolytics at age 43 on mental disorder at age 53, compared with those who received no pharmaceutical treatment.<sup>22</sup> Odds ratios of less than 1 indicate beneficial effects of treatment.

All calculations involving propensity scores used the program PSCORE for Stata 9.0.

## Results

There were 204 individuals with mental disorder at age 43, a prevalence of 7.0%. Among these, 45 were using an antidepressant or anxiolytic (22.1%); 23 were using an antidepressant only, 17 were using an anxiolytic only, and 5 were using both. Of these, 157 were followed-up 10 years later at age 53 (77.0%). There was a trend to suggest that those lost to follow-up might have had more severe symptoms at age 43 (mean PSF=44.2 *v.* 40.7, *P*=0.07); however, those lost to follow-up were no more likely to be using antidepressants or anxiolytics than those with complete data at age 53 (25.5% *v.* 21.0%, *P*=0.43). The remaining analyses include those 157 with follow-up data at age 53.

### Propensity-for-treatment with psychotropic medications

There were several differences between those treated with anxiolytics or antidepressants and those who were not (Table 1). In particular, those with a poorer mental state, including more severe symptoms and suicidal ideation, were more likely to be treated as were those with a history of mental disorder or psychiatric treatment.

All eight variables listed in Table 1 were included in a logistic regression model that calculated propensity-for-treatment (i.e. probability of treatment). This model included 140 of the 157 individuals; the 17 not included did not have complete data on all variables, but did not differ from those included with respect to mean PSF score (40.6 for those included, 41.8 for those not included, *P*=0.66) at age 43. This model explained 15% of the variance in likelihood of treatment, and balanced all predictive

**Table 1** Associations between predictors and treatment with psychotropic medication for those with mental disorder at age 43

	Prevalence of factor, n/N	Proportion being treated among those with factor, %	Proportion being treated among those without factor, %	OR for treatment (95% CI)
Current clinical characteristics				
More severe symptoms	20/157	45.0	17.5	3.9 (1.4-10.3)*
Suicidal ideation	24/155	41.7	17.6	3.4 (1.3-8.5)*
Sleep difficulties	76/157	25.0	17.3	1.6 (0.7-3.5)
Alcohol misuse	23/157	21.7	20.9	1.1 (0.4-3.1)
Clinical history				
Mental disorder at age 36	34/142	29.4	16.7	2.1 (0.9-5.1)
Psychiatric treatment between age 16 and 36	22/157	40.9	17.8	3.2 (1.2-8.3)*
Psychiatric hospitalisation up to age 43	16/157	25.0	20.6	1.3 (0.4-4.3)
Self-reported history of nervous trouble	110/155	28.2	4.4	8.4 (1.9-37.0)*

\**P*<0.05.

variables between those treated and those untreated within quintiles of the propensity score.

### Outcome of treatment with medications

Before adjusting for propensity-for-treatment, those treated with psychotropic medications at age 43 were no more or less likely to have a mental disorder at age 53 than those not treated with medications (Table 2). The lack of effect was also similar across the secondary outcomes.

After adjusting for propensity-for-treatment, those treated with antidepressants or anxiolytics were significantly less likely to have mental disorder 10 years later (odds ratio (OR)=0.3, 95% CI 0.1–1.0). This relationship held when the definition of mental disorder was expanded to include sub-threshold symptoms at age 53 (Table 2). In addition, linear regression suggested that those treated with antidepressants or anxiolytics had, on average, a GHQ total score that was about three points lower ( $\beta=-3.0$ , 95% CI  $-6.3-0.2$ ) than those not treated with medications.

Among those treated with antidepressants or anxiolytics at age 43, 24.2% were using one or both at age 53. In all cases, conclusions regarding effect of treatment on subsequent mental disorder were unchanged after adjusting for current medication use at the time of outcome assessment. Although statistical power to detect drug-specific differences was minimal, the likelihood of mental disorder was similar for antidepressants (OR=0.3, 95% CI 0.05–1.2) and anxiolytics (OR=0.2, 95% CI 0.02–1.7).

There were no significant effects of antidepressant or anxiolytic use at age 43 on sleeping difficulties, alcohol misuse or symptoms of psychosis at age 53.

### Sub-threshold mental disorder

A separate analysis was performed on 156 individuals with sub-threshold mental disorder at age 43 years and follow-up data at age 53. Among these, only 10 (6.4%) were using an antidepressant or anxiolytic. The same eight variables listed in Table 1 were used to calculate the propensity-for-treatment among these individuals. This second propensity model included 121 individuals and explained 17% of the variance in likelihood of treatment. Before adjusting for propensity-for-treatment, individuals who were treated with antidepressants or anxiolytics were more likely to have mental disorder 10 years later (OR=5.2, 95% CI 1.2–21.5). After adjusting for propensity-for-treatment, the likelihood of future mental disorder was similar, but was no longer statistically significant (OR=3.9, 95% CI 0.8–18.9).

have a long-term beneficial effect. Individuals with mental disorder were significantly less likely to have mental disorder 10 years later if they were using antidepressants or anxiolytics. These positive effects, however, were not apparent among individuals with less severe symptoms.

A particularly important predictor of prognosis may be the effectiveness of initial treatment. Pintor *et al* followed individuals for 2 years after treatment of depression and found that only 15% of those whose symptoms remitted completely during initial treatment had a relapse, while 68% of those who had partial relief of symptoms initially had a relapse during the follow-up period.<sup>23</sup> This suggests that the mode of treatment delivered may be less important than the fact that an effective treatment is delivered at all,<sup>24</sup> which was supported in this study by the fact that individuals who were treated with antidepressants had similar outcomes to those treated with anxiolytics.

These results may appear to support systematic reviews showing that maintenance therapy with antidepressants helps prevent relapses of depressive episodes;<sup>3</sup> however, such preventive effects presume continuation of therapy. Given that less than a quarter of individuals who were using antidepressants or anxiolytics at age 43 were using them at age 53, it is unlikely the results of our study can be explained by long-term maintenance therapy. It appears more likely that the results can be explained by an initial willingness to be treated, potential successful initial treatment and an increased likelihood that these patients would seek and accept help when encountering symptoms of depression and anxiety in the future. Individuals who have been treated for mental disorder in the past are more likely to seek and receive treatment for current symptoms,<sup>15,25,26</sup> and are more likely to believe that medical interventions will be helpful for depression.<sup>27</sup> Those who believe that antidepressants will be helpful are also more likely to use them.<sup>28</sup>

These findings are particularly interesting in the context of a World Health Organization study of outcomes of depression in primary care.<sup>29</sup> Results from that study suggested that mental health outcomes for help-seeking patients 12 months after their initial visit to a primary care physician were similar regardless of whether the patient's depressive symptoms were identified, implying that specific treatment had no long-term benefit. Those being treated in primary care may be comparable with those with sub-threshold symptoms in our study, and the lack of long-term effect we observed among this group may point to equivalent or similar initial short- or medium-term outcomes between those with less severe symptoms who are treated with antidepressants or anxiolytics and those who are not.

It is notable that long-term differences between those treated and those not treated were not apparent before accounting for propensity-for-treatment. Previous research has shown that individuals with more severe symptoms<sup>12,13</sup> and individuals

## Discussion

### Findings and related research

Results from this study suggest that treatment with antidepressants or anxiolytics during an episode of mental disorder may

**Table 2** Outcomes at age 53 for psychotropic medication use at age 43 among those with mental disorder

Outcomes at age 53	OR for treatment effect (95% CI)	
	Before propensity adjustment (n=140)	After propensity adjustment <sup>a</sup> (n=140)
Primary outcome		
Mental disorder	0.7 (0.2–2.1)	0.3 (0.1–1.0)*
Secondary outcomes		
Mental disorder including sub-threshold symptoms	0.7 (0.3–1.7)	0.3 (0.1–1.0)*
Sleeping difficulties	0.8 (0.3–2.0)	0.6 (0.2–1.6)
Alcohol misuse	1.3 (0.4–4.2)	0.9 (0.2–3.5)
Symptoms of psychosis	1.5 (0.7–3.6)	1.4 (0.6–3.5)

a. See Table 1 for factors included in adjustment for propensity for treatment.  
\*P<0.05.

with a history of mental illness<sup>13,14</sup> have a poorer long-term prognosis in depression and are more likely to have relapse episodes. As severity of symptoms and history of psychiatric illness are also associated with likelihood of treatment,<sup>15</sup> they confound the observed relationship between treatment and outcome. Observational studies can be useful in the investigation of short- and long-term effects of psychotropic medications, but such other, related prognostic factors must be accounted for.

## Methodological considerations

There are several limitations to this study. Most important is that although propensity scores balance all identified confounders of the treatment–outcome relationship, they do not balance unmeasured confounders in the way that is, theoretically, done with randomised controlled trials.<sup>5,22</sup> The propensity-for-treatment model only accounted for 15% of the variance in likelihood of treatment; consequently, there must be unmeasured factors that influence treatment. However, this is only an important limitation if these unmeasured factors also influence prognosis. We were able to balance eight covariates between the treated and untreated groups, including important factors such as severity of symptoms and history of illness that are strongly associated with prognosis.<sup>12–14</sup> Nevertheless, it is possible that unmeasured factors could explain the observed association between antidepressant and anxiolytic use and better long-term mental health. One such factor is neuroticism, which is associated with both help-seeking behaviour<sup>30</sup> and poorer prognosis for depression and anxiety.<sup>13</sup> Since individuals who were neurotic were more likely to be in the treatment group, and more likely to have a poor outcome, the treatment effect observed in this study should be a conservative estimate without neuroticism included in the propensity model. Still, other unmeasured factors could have biased our results in the other direction, making the observed effects an over-estimation of the true effect.

Another limitation is that we have no data on what happened between the initial assessment and the outcome 10 years later. It is unknown for how long individuals continued their psychotropic medication use. In addition, it should be noted that the initial assessment was in 1989, when selective serotonin reuptake inhibitors were not as common as they are today,<sup>25</sup> so the outcomes described may not be generalisable to currently prescribed medications.

A final limitation is missing data. There were 64 of 204 individuals who were excluded due to missing data on predictors of treatment or missing follow-up data. It is possible that these individuals were systematically different from those who remained in the study; in particular, those with more severe symptoms may have dropped out. Similarly, this sample was not large enough to consider a larger number of covariates that may influence the relationship between treatment and long-term outcome. Future studies, with greater statistical power, could include numerous other factors that may vary between those who are treated with psychotropic medications and those who are not such as socio-demographic or personality characteristics.

These limitations, however, are offset by some notable strengths. The sample was population-based, and the follow-up period is much longer than any comparable outcome studies of antidepressants and anxiolytics. Given the continuing under-treatment of depression in Britain and elsewhere,<sup>25,31</sup> the long-term effects demonstrated in this study may have considerable implications for public health policy.

**Ian Colman**, PhD, Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, Canada; **Tim J. Croudace**, PhD, Department of Psychiatry, University of Cambridge, Cambridge, UK; **Michael E. J. Wadsworth**, PhD, FFPH, **Diana Kuh**, PhD, Medical Research Council National Survey of Health and Development, Department of Epidemiology and Public Health, University College London Medical School, London, UK; **Peter B. Jones**, MD, PhD, Department of Psychiatry, University of Cambridge, Cambridge, UK.

**Correspondence:** Ian Colman, Department of Public Health Sciences, School of Public Health, University of Alberta, 13-130D Clinical Sciences Building, Edmonton, Alberta T6G 2G3, Canada. Email: ian.colman@ualberta.ca

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## Poems by doctors

### Rapunzel

Jason David Eubanks

Her pasty white flesh is prodigious,  
Enough to completely dislocate her knee  
With a simple fall from standing,  
Her pulseless leg lying frightened  
On the table where this grown woman  
Whimpers like a child –  
But she is known most for her hair,  
Or the absence thereof,  
The tiny islands of centimetric stubble  
Surrounded by a sea of battered scalp  
Raped of its rolling, wavy color  
By desperate hands –  
*Trichotillomania*,  
They say under hushed breaths,  
*And some will even eat it*,  
The trichobezoar swimming in the  
Sewage of the gluttonous bowels –  
*Rapunzel, Rapunzel, let down your hair* –  
In your solitary tower  
You have pulled the braided ladder  
Down to the last few follicles  
In hopes the enchantress would leave you,  
Alone –  
You are alone,  
A spectacled-bald and banished Rapunzel  
Who screams in horror  
As my pulling hands deliver you  
A stable reduction.

Jason David Eubanks, MD, is a graduate of Case Western Reserve University School of Medicine in Cleveland, Ohio and a current Spine Fellow in Orthopaedic Surgery at the University of Pittsburgh Medical Center. His poetry has been published in numerous literary and medical journals. Among others, these include *JAMA*, *Annals of Internal Medicine*, *Annals of Emergency Medicine* and *The Pharos*. Dr Eubanks' book, *Rotations: a Medical Student's Clinical Experience*, is a collection of poems, the first of its kind, written about the process of becoming a doctor. *Rapunzel* represents one of Dr Eubanks' more recent psychiatric poems. It emanates from a first-hand encounter with a patient as a resident in the trauma bay.

Researched by Femi Oyeboode.

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